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Dated: September 16, 2002

Signature: Staci Harris

Staci V. Harris

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:  
Lars Abrahmsen et al.

Docket No.: HO-P01525US0

Application No.: 08/765,695

Group Art Unit: 1644

Filed: July 25, 1997

Examiner: R. Schwadron

For: A CONJUGATE BETWEEN A MODIFIED  
SUPERANTIGEN AND A TARGET-SEEKING  
COMPOUND AND THE USE OF THE CONJUGATE

**TRANSMITTAL OF THIRD AMENDED APPELLANT'S BRIEF**

**Attention: Board of Patent Appeals and Interferences**  
Commissioner for Patents  
Washington, DC 20231

Dear Sir:

Appellants hereby submit an original and two copies of this amended Appeal Brief to the Board of Patent Appeals and Interferences in response to notice of non-compliant Appeal Brief, which was mailed on August 16, 2002. Appellants are filing this amended Brief in accordance with 37 CFR § 1.192(d). Appellants assert that the amended Brief satisfies 37 CFR § 1.192(c).

Appellants do not believe that there are any additional fees for the filing of this amended Appeal Brief. If however, Appellants are not correct, then the Appellants hereby authorize the Commissioner to deduct any fees for filing of the amended Appeal Brief from the Fulbright & Jaworski Deposit Account No. 06-2375, Order No. 09804877.

Dated:

September 16, 2002

Respectfully submitted,

By Melissa W. Acosta

Melissa W. Acosta

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BOARD OF PATENT APPEALS AND INTERFERENCES

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Dated: September 16, 2002

Signature: Staci V. Harris

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(PATENT)

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**Attention: Board of Patent Appeals and Interferences**  
Commissioner for Patents  
Washington, DC 20231

Dear Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences in response to the notice of non-compliant Appeal Brief, which was mailed on August 16, 2002. A Second Amended Appeal Brief was filed on May 29, 2002. An Amended Appeal Brief was filed on January 29, 2002. The original Appeal Brief was filed in response to the Advisory Action dated July 24, 2001 and the final Office Action dated April 17, 2001. This brief is in furtherance of the Notice of Appeal, filed in this case on August 15, 2001.



## **I. REAL PARTY IN INTEREST**

The real party in interest for this appeal is the assignee, Pharmacia & Upjohn AB.

## **II. RELATED APPEALS AND INTERFERENCES**

There are no other appeals or interferences, which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

## **III. STATUS OF CLAIMS**

Claims 14-51 were originally filed in the present application. During prosecution, claims 52-57 were added, claims 14-35, 37-52 were canceled, claims 53-57 were withdrawn from consideration but not canceled and claim 36 was amended. The claim on appeal is independent claim 36. Appendix A contains the claim under appeal, in what Appellants believe to be the correct status.

## **IV. STATUS OF AMENDMENTS**

Appellants filed an Amendment After Final, which was filed on May 29, 2002, to cancel claims 37, 38, 44-47 and 52. The Amendment was entered by the Examiner as indicated by the Advisory Action, which was mailed August 13, 2002. Yet further, Appellants filed an Amendment After Final, which was filed on June 25, 2001, to amend the Abstract. The Amendment to the Abstract was entered by the Examiner as indicated by the Advisory Action, which was mailed on July 24, 2001.

## **V. SUMMARY OF INVENTION**

The present invention uses a conjugate comprising a mutated superantigen to treat a disease or a condition in a mammal. The mutated superantigens are based upon Appellant's discovery that different regions of superantigens are responsible for binding the MHC class II antigens. Mutations in these regions can affect MHC class II binding resulting in decreased toxicity of the superantigens while retaining the therapeutic effects of the superantigens. For

example, some of the therapeutic effects include activation of T lymphocytes which results in selective lysis of cells. *See* Specification p. 4, lns., 6-15; p. 9, lns., 18-23; Table III; and p. 22, lns., 4-10.

## **VI. ISSUES**

The issues for the Board's consideration are:

Whether claim 36 is properly rejected under 35 U.S.C. § 103(a) as being unpatentable over Dohlsten *et al.*, PNAS USA 88:9287-9291(1991).

Whether the information disclosure statement complies with 37 CFR § 1.97(c).

## **VII. GROUPING OF CLAIMS**

Independent claim 36 is the only claim on appeal, thus, Appellants argue for patentability of the subject matter of claim 36 herein.

## **VIII. ARGUMENTS**

### **A. Claim 36 is non-obvious.**

The Examiner has rejected claim 36 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Dohlsten *et al.*, PNAS USA 88:9287-9291, 1991. The Examiner contends that Dohlsten *et al.*, suggests making mutations in the C-terminal region of superantigens in order to reduce class II MHC antigen binding. Appellants respectfully traverse this rejection.

#### *i. A Non-enabling Reference Is Not Available Prior Art*

The Manual of Patent Examining Procedures (MPEP) sets forth the guidelines or conditions for patentability of non-obvious subject matter under 35 U.S.C § 103 in MPEP § 2141.01. This section clearly states that “before answering Graham’s content inquiry, it must be known whether a patent or publication is in the prior art under 35 U.S.C. § 102. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1025 (1987). Both the Federal Circuit Court and the court of Customs and Patent Appeals have directed the Patent Office to determine if the prior art reference is

available 35 U.S.C. § 102 as an enabling reference. See *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed Cir. 1985), and *In re LeGrice*, 301 F.2d 939, 133 USPQ 365, 371 (CCPA 1962).

Appellants have clearly shown that Dohlsten *et al.*, is a non-enabling reference under Section 102. Specifically, Dohlsten *et al.*, does not teach or suggest making mutations in any specific region of a superantigen in order to affect class II MHC antigen binding. In addition, the Office has acknowledged, in the Office Action of August 16, 1999, page 5, that “Dohlsten *et al.*, does not teach that the superantigen portion of the conjugate has been mutated to show a modified ability to bind class II MHC antigen.”

Despite this acknowledgment, the Office has continued to erroneously conclude that Dohlsten *et al.*, teaches which regions of superantigens are indicated in MHC class-dependent binding. The Office has used the following statements as the premise of its erroneous conclusion: i)

it would be of importance to further perturb MHC class II-dependent CTL activity by reducing the binding of the C215-SEA conjugate for MHC class II molecules

(Dohlsten *et al.*, page 9291, column 1);

and ii)

MHC class II binding has been localized to the C-terminal.

(*Id.*).

Appellants assert that these statements, taken alone or in combination, do not teach which regions of superantigens are indicated in class II MHC binding. In fact, Appellants contend that Dohlsten *et al.*, did not know (nor could they teach) which regions of superantigens are indicated in class II MHC binding. For example, the statement following the two statements that the Office cites above in Dohlsten *et al.*, states that:

The determination of the amino acids necessary for MHC class II binding may provide a rationale to obtain mAb-SEA conjugates with preserved T-cell-activating properties but totally devoid of binding to MHC class II molecules.

(Dohlsten *et al.*, page 9291, column 1).

This statement shows that Dohlsten *et al.*, merely states that the amino acids need to be determined. Thus, Dohlsten *et al.*, does not provide a guideline to determine which amino acids are necessary for binding nor does Dohlsten *et al.*, provide a guideline for mutating superantigens to modify their ability to bind to MHC class II.

In contrast to Dohlsten *et al.*, the present invention teaches for the first time the specific regions of superantigens that are responsible for binding MHC class II antigens and that mutations in these regions affect MHC class II binding. *See* specification p. 23, lns., 12-15.

Yet further, Appellants assert that there was an immense body of scientific literature at the time the application was filed that suggested that the MHC class II binding region of superantigens resided in the N-terminal domain of superantigens and not the C-terminal domain (*see* Kim *et al.*, Science, 1994, 266:1870 (TSST-1 MHC class II binding); and Jardetzky *et al.*, Nature, 1994, 368:711 (SEB MHC class II binding) (Appendix D)). Thus, Appellants assert that Dohlsten *et al.*, which indicated to look in the C-terminal domain, in fact, taught away from the thinking of skilled artisans at the time the application was filed. Since Dohlsten *et al.*, taught away from other scientific literature, a skilled artisan would not have used Dohlsten *et al.*, as a basis for routine experimentation. Thus, Dohlsten *et al.*, is a non-enabling reference under 35 U.S.C. § 102 because Dohlsten *et al.*, does sufficiently describe the claimed invention to have placed the public in possession of it. *In re LeGrice*, 301 F.2d 939, 133 USPQ 365, 371 (CCPA 1962).

ii. *Prima facie Case of Obviousness Must be Established*

The Manual of Patent Examining Procedures (MPEP) sets forth the guidelines to establish a *prima facie* case of obviousness under 35 U.S.C § 103 in MPEP § 2143.3. This section states that three basic criteria must be met to establish a *prima facie* case of obviousness. The three criteria are:

- 1) a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
- 2) a reasonable expectation of success; and
- 3) the prior art reference must teach or suggest all the claim limitations.

In light of the above criteria, Appellants assert that the Office has not established a *prima facie* case of obviousness to reject the claims under 35 U.S.C. 103. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). A *prima facie* case necessitates disclosure of the source for either a suggestion or motivation to modify a cited reference to produce the present invention, and a reasonable expectation of success of producing the claimed invention. *Dohlsten et al.*, does not provide a suggestion nor does it provide a reasonable expectation of success of producing a mutated superantigen having modified binding ability. This is clearly indicated by the acknowledgement of the Office that *Dohlsten* does not teach a mutated superantigen having a modified ability to bind to class II MHC antigens. (See Office Action dated August 16, 1999, p. 5)

The Board has held that evidence, rather than conjecture, is necessary in order to establish a *prima facie* case. *See Ex parte Yamamoto*, 575 USPQ2d 1382, 1383, 1384 (Bd. Pat. App. Inf. 2000) (unpublished decision). Appellants assert that the Office has not provided sufficient evidence to establish a *prima facie* case. Appellants assert that it is mere conjecture on the part of the Office that one of skill in the art would be able to identify the region without undue experimentation. If anything, *Dohlsten et al.*, demonstrates the need to

identify the regions in superantigens that are necessary for MHC class II binding, but does not provide reasonable enablement for one of skill in the art to obtain these regions without undue experimentation.

Therefore, in view of the above arguments that Dohlsten *et al.*, is a non-enabling reference and that the Office has not established a *prima facie* case of obviousness based on Dohlsten *et al.*, Appellants respectfully request that the Board overturn the rejection of the claims for non-obviousness.

**B. IDS complies with 37 CFR 1.97(c).**

Appellants submitted two references (Kim *et al.*, Science, 1994, 266:1870 and Jardetzky *et al.*, Nature, 1994, 368:711) (Appendix D) in a Supplemental Information Disclosure Statement to support arguments that, at the time the present application was filed, one skilled in the art assumed that class II MHC binding was in the N-terminal domain of superantigens. However, the Office contends that the Supplemental Information Disclosure Statement did not comply with 37 CFR § 1.97 (c), and thus refused to review the references.

Appellants respectfully request that the Board consider the references. Appellants assert that the Supplemental Information Disclosure Statement is in compliance with 37 CFR § 1.97 (c) because the appropriate fees were submitted with the filing of the Notice of Appeal on August 15, 2001.

**IX. CONCLUSION**

Appellants have provided arguments that overcome the pending rejections. Appellants respectfully submit that the Office's conclusions that the claims should be rejected are unwarranted. It is therefore requested that the Board overturn the Office's rejections.

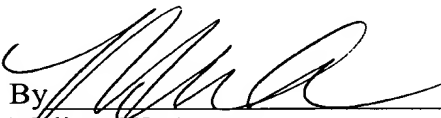
Appellants are filing this Third Amended Brief in accordance with 37 CFR § 1.192(d). Appellants assert that the Third Amended Brief satisfies 37 CFR § 1.192(c). Appellants do not believe that there are any additional fees for the filing of this Third

Amended Appeal Brief. If however, Appellants are not correct, then the Appellants hereby authorize the Commissioner to deduct any fees for filing of the amended appeal brief from the Fulbright & Jaworski Deposit Account No. 06-2375, Order No. 09804877.

Please date stamp and return the enclosed postcard to evidence receipt of this document.

Dated: *September 16, 2002*

Respectfully submitted,

By   
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## **APPENDIX A**

### **Claim Involved in the Appeal of Application Serial No. 08/765,695**

36. A method for the treatment of a disease condition in a mammal, which condition means the presence of specific cells that are associated with the condition by the expression of a disease specific cell surface structure, wherein one administers to the mammal a therapeutically effective amount of covalent conjugate that is able to activate T lymphocytes to lyse cells that carry the disease specific cell surface structure and comprises:
- a. a biospecific affinity counterpart that is capable of binding to said surface structure, and
  - b. a peptide that
    - i. contains an amino acid sequence that is derived from a superantigen selected from the group consisting of staphylococcal enterotoxin A, B, C<sub>1</sub>, C<sub>2</sub>, D and E,
    - ii. has the ability to bind to a V $\beta$  of a T cell receptor, and
    - iii. has been mutated to show a modified ability to bind to MHC class II antigens compared to the superantigens from which the peptide is derived.



## **APPENDIX B**

tiffs who vindicate substantive rights in court. "There is no suggestion in the congressional history of 42 U.S.C. § 1988, nor in the cases that have applied it, that it ought to be read in a niggardly way." *Smith v. Thomas*, 687 F.2d 113, 116 (5th Cir.1982). We do not do so today. The injunction granted below properly safeguarded important First Amendment rights. Finding that this injunction was granted on the central substantive issue and yielded the practical relief sought by plaintiffs, we hold that plaintiffs were prevailing parties entitled to an award of attorney's fees under 42 U.S.C. § 1988. We remand this cause to the district court for a hearing and award of reasonable attorney's fees or an explanation of special circumstances rendering the award of such fees unjust.

REVERSED and REMANDED.

ANDERSON, Circuit Judge, dissenting:

I agree with the majority opinion that the "central issue presented by plaintiffs' complaint was that the solicitation permit requirements imposed upon the Unification Church in its outdoor solicitations were unconstitutional." I also agree that the preliminary injunction afforded relief to plaintiffs on this central issue. I also agree that the summary judgment later entered by the court, granting plaintiffs relief only as to indoor solicitation, did not constitute "a favorable judgment on the central issue in the case." At this point, my agreement with the majority opinion ends. I disagree with the majority's conclusion that the relief on the central issue of outdoor solicitation obtained by plaintiffs in the preliminary injunction somehow survives the entry of the later summary judgment. The majority reaches this conclusion notwithstanding the fact that the summary judgment opinion clearly rejected plaintiffs' claim for relief with respect to outdoor solicitation, holding that "the record shows no discrimination by the City in requiring

permits for outdoor solicitation." 538 F.Supp. 514, 517 (S.D.Fla.1984). Whether or not a formal judgment was entered to this effect, as a practical matter, it is clear that the relief obtained by plaintiffs in the preliminary injunction on the crucial issue in the case was vitiated upon entry of the later summary judgment. *Doe v. Busbee*, 684 F.2d 1375 (11th Cir.1982), squarely holds that a plaintiff is not a prevailing party when it obtains initial relief in the district court which is later vacated. In this case, just as in *Doe v. Busbee*, the initial relief obtained by plaintiffs on the crucial issue was vitiated by later court action. I disagree with the majority's conclusion that the instant case is distinguishable from *Doe v. Busbee*, because I disagree with the majority's conclusion that the initial relief obtained by plaintiffs in the preliminary judgment somehow survived the later summary judgment.<sup>1</sup>

With respect, I dissent.



PANDUIT CORPORATION, Appellant,

v.

DENNISON MANUFACTURING  
CO., Appellee.

Appeal No. 85-1144.

United States Court of Appeals,  
Federal Circuit.

Jan. 23, 1987.

Manufacturer of plastic cable ties brought patent infringement action against competitor. The United States District Court for the Northern District of Illinois,

1. Plaintiffs apparently conceded below that the amendment to the ordinance mooted the case. However, even if the instant suit were a catalyst motivating the amendment, the amended ordi-

nance provided no relief with respect to the central issue of outdoor solicitation. The plaintiffs' concession may have been more in the nature of an abandonment.

John F. Grady, Chief Judge, held patent claims invalid. The Court of Appeals, 774 F.2d 1082, reversed, but the Supreme Court, 106 S.Ct. 1578, vacated that ruling and remanded. On remand, the Court of Appeals, Markey, C.J., held that: (1) determination that invention would or would not have been "obvious" is conclusion of law, and (2) competitor failed to carry its burden of proving that claimed inventions would have been obvious.

Affirmed in part, reversed in part, and remanded.

**1. Patents ⇐324.5, 324.55(2)**

On review of judgment invalidating patent based on conclusion of obviousness, Court of Appeals must consider not only whether there is legal error, but also whether underlying findings are either nonprobative, clearly erroneous, or both. 35 U.S.C.A. § 103.

**2. Patents ⇐324.60**

If district court does not make findings necessary to resolution of obviousness question in patent dispute, and legal error is present, appellate court should vacate in view of that legal error and remand for district court to make missing findings; if unassailable findings are made, but can not support appealed judgment under proper application of law, appellate court may vacate or reverse, but not make its own findings. 35 U.S.C.A. § 103.

**3. Federal Courts ⇐850**

If findings necessary to support legal conclusion are clearly erroneous, conclusion can not stand.

**4. Patents ⇐324.60**

To obtain reversal without remand of decisions invalidating patent for obviousness, appellant-patentee must convince Court of Appeals that patent challenger failed at trial to carry its statutory burden of proving by clear and convincing evidence sufficient facts to support obviousness conclusion; one way to do that is to show that proper application of law to unassailable findings compels reversal, while another is to show that findings on which obviousness

conclusion rested are clearly erroneous and that nothing of record warrants further exercise of fact-finding function or indicates any possibility that appealed judgments might be sustained by such exercise. 35 U.S.C.A. §§ 103, 282.

**5. Patents ⇐16(1)**

Analysis of whether patent is invalid for obviousness begins with key legal question, i.e., what is the invention claimed; another key preliminary legal inquiry is determining what is prior art. 35 U.S.C.A. § 103.

**6. Patents ⇐16(2)**

In determining scope and content of prior art on question of obviousness, prior patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention in suit. 35 U.S.C.A. § 103.

**7. Patents ⇐16(2)**

In determining scope and content of prior art on question of obviousness, elements of separate prior patents cannot be combined when there is no suggestion of such combination anywhere in those patents. 35 U.S.C.A. § 103.

**8. Patents ⇐16(4)**

Court should avoid hindsight in determining scope and content of prior art on question of obviousness. 35 U.S.C.A. § 103.

**9. Patents ⇐314(5)**

Determination that invention would have been obvious when it was made to one of ordinary skill in the art is conclusion of law based on facts; degree to which it is one of fact is solely that degree required to erect foundation of facts capable of supporting conclusion, those facts having been found by applying correct legal standards and expressed in findings free from clear error and based on clear and convincing evidence. 35 U.S.C.A. § 103.

**10. Patents ⇐314(5)**

Determination that invention would not have been obvious when it was made to one of ordinary skill in the art is conclusion

of law which is in place at outset of trial; factual questions are those raised by patent challenger in effort to replace existing conclusion with a contrary one, and those, if any, raised by patentee in rebuttal of challenger's case. 35 U.S.C.A. § 103.

#### 11. Patents ⇨324.55(4)

In review of question of patent obviousness, appellate "clearly erroneous" standard is applicable to all findings on scope and content of prior art, differences between prior art and claimed invention, level of skill, and objective evidence; last may include commercial success due to invention, failure of others, long-felt need, movement of the skilled in different direction, skepticism of experts, copying invention in preference to prior art, and other events proved to have actually happened in real world. 35 U.S.C.A. § 103; Fed.Rules Civ.Proc.Rule 52(a), 28 U.S.C.A.

#### 12. Patents ⇨314(6)

It is neither necessary nor appropriate for court to declare patent valid, as statute makes patent presumptively valid when issued; trial court is required only to say whether patent challenger carried its burden of establishing invalidity in particular case before court. 35 U.S.C.A. § 282.

#### 13. Patents ⇨312(1<sup>1/2</sup>)

Statutory presumption of patent validity is applicable to all of many bases for challenging patent's validity, and when sole challenge is allegation of obviousness, presumption is that invention would not have been obvious. 35 U.S.C.A. §§ 103, 282.

#### 14. Patents ⇨314(6)

Determination of anticipation may be reached by comparing only claims and prior art disclosures submitted by patent challenger. 35 U.S.C.A. § 102.

#### 15. Patents ⇨314(6)

Determination that patent challenger has not carried its burden of showing obviousness of invention may be reached on consideration of only evidence submitted by patent challenger; determination that challenger has carried burden of establishing obviousness, however, requires full consid-

eration of any objective evidence of nonobviousness presented in rebuttal. 35 U.S.C.A. §§ 103, 282.

#### 16. Patents ⇨312(6)

Challenger of patent on plastic cable ties failed to carry its burden of proving that those cable ties were "obvious" prior to time of patent. 35 U.S.C.A. §§ 103, 282.

#### 17. Patents ⇨314(2)

Valuation of worth of inventor's contribution is left to public, not to judiciary in determining patentability; judge is nowhere authorized to declare patent invalid on his or her personal evaluation.

#### 18. Patents ⇨157(1)

In interpreting patent claims, district court committed fundamental legal error in analyzing each by single-word description of one part of claimed invention; in patent law, word means nothing outside claim and description in specification.

#### 19. Patents ⇨324.55(4)

When prior art is compared with erroneously interpreted claims, in context of "obviousness" determination, findings of differences between prior art and claims will necessarily be clearly erroneous. 35 U.S.C.A. §§ 103, 282.

#### 20. Patents ⇨157(1)

In interpreting claims in context of "obviousness" determination with regard to plastic cable ties, district court erred in reducing claims to single element, i.e., "teeth," "hinge," and "ledge," while dismissing novel structural claim limitations that defined disposition, positioning, relationship, and operation of elements in claim.

---

Charles F. Pigott, Jr., Pigott, Gerstman & Giehooly, Ltd., of Chicago, Ill., argued for appellant. With him on the brief was Charles R. Wentzel, Panduit Corp., of Tinley Park, Ill., of counsel.

James P. Ryther, McDougall, Hersh & Scott, of Chicago, Ill., argued for appellee. With him on the brief was Clyde F. Willian, Willian Brinks Olds Hofer Gilson & Lione,

Ltd., of Chicago, Ill. Also on the brief were James P. Hume, James B. Blanchard, Robert L. Harmon, John J. Pavlak, Cynthia A. Homan, Richard A. Kaplan and Glen P. Belvis, of Willian Brinks Olds Hofer Gilson & Lione, Ltd., of Chicago, Ill., of counsel.

Donald S. Chisum, University of Washington School of Law, of Seattle, Wash., was on the brief for Amicus Curiae, American Intellectual Property Law Ass'n. Also on the brief was Thomas F. Smegal, President, American Intellectual Property Law, of Arlington, Va.

Before MARKEY, Chief Judge,  
COWEN, Senior Circuit Judge, and  
NEWMAN, Circuit Judge.

MARKEY, Chief Judge.

On remand from the Supreme Court. Having considered the record, appealed judgment, district court's findings and application of law, arguments in this court and the Supreme Court, and invited briefs of the parties and *amicus* American Intellectual Property Law Association, we respond to the remand and again affirm the judgment on the 35 U.S.C. § 102(g) defense and reverse the judgment on the 35 U.S.C. § 103 defense.

#### *The Remand*

In remanding, *Dennison Manufacturing Co. v. Panduit Corp.*, — U.S. —, 106 S.Ct. 1578, 89 L.Ed.2d 817, 229 USPQ 478 (1986), *vacating*, 774 F.2d 1082, 227 USPQ 337 (Fed.Cir.1985), the Supreme Court said:

Petitioner contends that the Federal Circuit ignored Federal Rule of Civil Procedure 52(a) in substituting its view of factual issues for that of the District Court. In particular, petitioner complains of the rejection of the District Court's determination of what the prior art revealed and its findings that the differences identified between respondent's patents and the prior art were obvious.

Petitioner's claims are not insubstantial. As this Court observed in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 [86

S.Ct. 684, 693-94, 15 L.Ed.2d 545, 556-57], 148 USPQ 459, 467 (1966):

"While the ultimate question of patent validity is one of law, ... the § 103 condition [that is, nonobviousness] ... lends itself to several basic factual inquiries. Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unresolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy."

This description of the obviousness inquiry makes it clear that whether or not the ultimate question of obviousness is a question of fact subject to Rule 52(a), the subsidiary determinations of the District Court, at the least, ought to be subject to the Rule.

The Federal Circuit, however, did not mention Rule 52(a), did not explicitly apply the clearly-erroneous standard to any of the District Court's findings on obviousness and did not explain why, if it was of that view, Rule 52(a) had no applicability to this issue. We therefore lack an adequate explanation of the basis for the Court of Appeals' judgment: most importantly, we lack the benefit of the Federal Circuit's informed opinion on the complex issue of the degree to which the obviousness determination is one of fact. In the absence of an opinion clearly setting forth the views of the Court of Appeals on these matters, we are not prepared to give plenary consideration to petitioner's claim that the decision below cannot be squared with Rule 52(a). Instead, we grant the petition for certiorari, vacate the judgment and remand the

case to the Court of Appeals for further consideration in light of Rule 52(a).

106 S.Ct. at 1579, 89 L.Ed.2d at 821, 229 USPQ at 479.

### *Opinion on Remand*

Reversal of the district court's judgment on the § 103 defense was and is compelled because of legal error, because a first set of clearly correct and unchallenged findings requires that the conclusion of nonobviousness, 35 U.S.C. § 282,<sup>1</sup> must remain untrammelled and because a second set of findings, some nonprobative, some clearly erroneous, is unable to support, intrinsically and in light of the first set, the district court's conclusion of obviousness.

The Background section of our earlier opinion noted error in the second set of findings but did not label it clearly erroneous, Rule 52(a), and did not expressly indicate that the noted error was not the basis for reversal set forth in the Opinion section, thus raising a question respecting the basis for our judgment. That circumstance, regrettable because it has delayed a just end to this litigation, is here rectified.

[1, 2] On review of a judgment based on a conclusion of obviousness under 35 U.S.C. § 103<sup>2</sup>, this court must consider not only whether there is legal error, but also whether the underlying findings are either nonprobative, or clearly erroneous, or both. If, unlike the present case, a district court had not made findings necessary to resolution of the § 103 question, and legal error were present, an appellate court would va-

cate in view of that legal error and remand for the district court to make the missing findings. *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 872-75, 228 USPQ 90, 97-99 (Fed.Cir.1985). If unassailable findings were made but could not support the appealed judgment under a proper application of law, an appellate court may vacate or reverse but not make its own findings. *Icicle Seafoods, Inc. v. Worthington*, — U.S. —, —, 106 S.Ct. 1527, 1530, 89 L.Ed.2d 739, 743 (1986).

[3] If findings necessary to support a legal conclusion are clearly erroneous, the conclusion cannot stand. If those facts were such as to permit only one of two possibilities, or if the burden of proving those necessary facts had been on appellee, reversal would not mean the appellate court found facts in defiance of Rule 52(a).<sup>3</sup> If, unlike the present case, appellee did not bear the burden below, a remand-requiring fact-finding function might remain.

[4] To obtain reversal without remand, an appellant-patentee must convince this court that the patent challenger failed at trial to carry its statutory burden, 35 U.S.C. § 282, of proving by clear and convincing evidence sufficient facts to support the obviousness conclusion. One way to do that is to show that a proper application of the law to unassailable findings compels reversal. Another is to show that the findings on which the obviousness conclusion rested are clearly erroneous and that nothing of record warrants a further exercise of the fact-finding function or indicates any

1. 35 U.S.C. § 282 reads in pertinent part:

*A patent shall be presumed valid.* Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim. *The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.* [Emphasis added.]

2. 35 U.S.C. § 103 reads in pertinent part:

Conditions for patentability; non-obvious subject matter

A patent may not be obtained though the invention is not identically disclosed or de-

scribed as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. That a question is legal does not, of course, free an appellate court to ignore Rule 52(a), to disregard the clearly erroneous standard, to make its own findings *de nov*, or simply to disagree on whim with the district court's legal conclusion.

possibility that the appealed judgment might be sustained by such exercise. Because the record here establishes that appellant has made both showings, reversal is required and there is no basis for remanding the case for new findings by the district court.

In this opinion:

Part I supplies our opinion on the remand inquiry ("the degree to which the obviousness determination is one of fact").

Part II treats Rule 52(a)'s applicability to § 103.

Part III examines the statutory burden of proof.

Part IV describes inventor Caveney's inventions and the effect of his claims.

Part V discusses our earlier opinion and the district court's approach to resolution of the § 103 issue in this case.

Part VI identifies the patent claims on appeal.

Part VII sets forth the district court's erroneous claim interpretations.

Part VIII discusses the findings in general.

Part IX reviews correct findings that compel a conclusion of nonobviousness.

Part X reviews nonprobative and clearly erroneous findings that underlay the appealed judgment.

The Appendix comments on parts of the Petition for Certiorari and Reply.

### *Part I*

#### *The Obvious-Nonobvious Question is One of Law*

##### *(a) Nature*

A § 103 determination involves fact and law. There may be these facts: what a prior art patent as a whole discloses; what it in fact disclosed to workers in the art;

what differences exist between the entire prior art, or a whole prior art structure, and the whole claimed invention; what the differences enabled the claimed subject matter as a whole to achieve; that others for years sought and failed to arrive at the claimed invention; that one of those others copied it; that the invention met on its merits with outstanding commercial success.

With the involved facts determined, the decisionmaker confronts a ghost, i.e., "a person having ordinary skill in the art," not unlike the "reasonable man" and other ghosts in the law. To reach a proper conclusion under § 103, the decisionmaker must step backward in time and into the shoes worn by that "person" when the invention was unknown and just before it was made. In light of *all* the evidence, the decisionmaker must then determine whether the patent challenger has convincingly established, 35 U.S.C. § 282, that the claimed invention as a whole would have been obvious at *that* time to *that* person. 35 U.S.C. § 103.<sup>4</sup> The answer to that question partakes more of the nature of law than of fact, for it is an ultimate conclusion based on a foundation formed of all the probative facts. If itself a fact, it would be part of its own foundation.

When findings on the foundational facts were not clearly erroneous this court must then determine whether the § 103 answer of the district court is supportable by those findings. As with other statutes, that determination engages this court in an exercise legal in nature.

##### *(b) Precedent*

The Supreme Court, the regional Circuit Courts of Appeals, and this court have consistently treated the question as one of law.<sup>5</sup>

4. Adherence to the statutes, §§ 103, 282, assures avoidance of a seat-of-the-pants judgment that the invention would "be" obvious at the time of trial to the judge or jury.

5. *E.g., Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 693, 15 L.Ed.2d 545, 556, 148 USPQ

459, 467 (1966); *In re McCarthy*, 763 F.2d 411, 412, 226 USPQ 99, 100 (Fed.Cir.1985); *Gardner v. TEC Systems, Inc.*, 725 F.2d 1338, 1344, 220 USPQ 777, 782 (Fed.Cir.) (in banc), *cert. denied*, 469 U.S. 830, 105 S.Ct. 116, 83 L.Ed.2d 60 (1984); *Roberts v. Sears, Roebuck & Co.*, 723 F.2d 1324, 1335, 221 USPQ 504, 514-15 (7th

*Graham's* statement, "the ultimate question of patent validity is one of law", has been widely interpreted as meaning that one answering the § 103 question is drawing a legal conclusion. And rightly so, because the validity issue in *Graham* turned on that answer and because of what the Court did in *Graham*. It disagreed with conclusions reached below, did not remand, described no finding as "clearly erroneous," and did not mention Rule 52(a).

The Court in *Graham* determined that the facts were (in No. 11) and were not (in Nos. 37 and 43) sufficient to support the lower courts' conclusions on the § 103 question. Similarly, unassailed and unassailable findings here compel our legal conclusion on that question.

### (c) Scholars

A survey of writings on "the vexing nature of the distinction between questions of fact and questions of law," *Pullman-Standard v. Swint*, 456 U.S. 273, 288, 102 S.Ct. 1781, 1790, 72 L.Ed.2d 66, 79 (1982), would unduly lengthen this opinion. Scholars who have dealt with the obviousness question unanimously view it as one of law.<sup>6</sup>

### (d) Effect

Like all legal conclusions, that under § 103 rests on a factual evidentiary foundation. As said in *Graham*, 383 U.S. at 17, 86 S.Ct. at 693, 15 L.Ed.2d at 556, 148 USPQ at 467, the question is determined "against" the "background" of answers to

Cir.1983) (in banc); *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1547, 220 USPQ 193, 197 (Fed.Cir.1983); *Sarkisian v. Winn-Proof Corp.*, 688 F.2d 647, 651 (9th Cir.1982) (in banc), cert. denied, 460 U.S. 1052, 103 S.Ct. 1499, 75 L.Ed.2d 930 (1983); *Julie Research Laboratories, Inc. v. Guildline Instruments, Inc.*, 501 F.2d 1131, 1135-36, 183 USPQ 1, 4-5 (2d Cir.1974); *Flour City Architectural Metals v. Alpina Aluminum Products, Inc.*, 454 F.2d 98, 105-06, 172 USPQ 341, 345-48 (8th Cir.1972); *Kolene Corp. v. Motor City Metal Treating, Inc.*, 440 F.2d 77, 81, 169 USPQ 77, 80 (6th Cir.), cert. denied, 404 U.S. 886, 92 S.Ct. 203, 30 L.Ed.2d 169 (1971); *Swoford v. B & W, Inc.*, 395 F.2d 362, 367, 158 USPQ 72, 76 (5th Cir.), cert. denied, 393 U.S. 935, 89 S.Ct. 296, 21 L.Ed.2d 272 (1968); *In re Sporck*, 301 F.2d 686, 690, 49 CCPA 1039, 1043, 133 USPQ 360, 364 (1962).

factual inquiries,—a description of how legal questions are normally determined.

One effect of considering the § 103 question one of law in this court is to facilitate a consistent application of that statute in the courts and in the Patent and Trademark Office (PTO).

To contribute to consistency in construing § 103, this court has affirmed judgments while noting noncontrolling misstatements of law and cautioning counsel that judgments are appealed, not opinion language.<sup>7</sup> Controlling misstatements of the legal criteria applicable to § 103 determinations, present in the district court's opinion language in this case, confirm the certain presence of reversible legal error. See 774 F.2d at 1091-1100, 227 USPQ at 342-49.

### (e) Decisional Process

The decisional process en route to a § 103 conclusion involves more than answers to the fact inquiries in *Graham*. It also involves: (1) legal determinations; and (2) legal standards for fact-finding.

#### (1) Legal Determinations

[5] Analysis begins with a key legal question—*what is the invention claimed?* Courts are required to view the claimed invention *as a whole*. 35 U.S.C. § 103. Claim interpretation, in light of the specification, claim language, other claims, and

Both parties and *amicus* agree that the question is one of law, though Dennison goes on to question whether it might be treated as one of fact.

6. See, e.g., 2 D. Chisum, *Patents*, § 5.04[3] (1986); 1 I. Kayton, *Patent Practice*, 5-11 (1985); 2 E.B. Lipscomb, *Walker on Patents*, § 6:4 (1985); 1 P. Rosenberg, *Patent Law Fundamentals*, § 9.02, at 9-12 to 9-12.1 (1985).

7. See, e.g., *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 317, 227 USPQ 766, 771 (Fed.Cir. 1985); *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556, 225 USPQ 26, 31 (Fed.Cir. 1985); *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548-50, 220 USPQ 193, 198-99 (Fed. Cir.1983).



prosecution history, is a matter of law<sup>8</sup> and will normally control the remainder of the decisional process. The district court's claim interpretation in this case constituted compound legal error not subject to Rule 52(a). See Part VII.

Another key preliminary legal inquiry is—what is the prior art? Before answering *Graham's* "content" inquiry, it must be known whether a patent or publication is in the prior art under 35 U.S.C. § 102,—a legal question.<sup>9</sup> In this case, for example, the '869 tie was not prior art and the district court's primary reliance on it was legal error not subject to Rule 52(a). See Part X.

### (2) Legal Standards

Clarity in the law requires universal application of the same legal standards to fact-finding functions performed en route to final § 103 conclusions.

[6–8] Among legal standards for determining scope and content of the prior art, for example, are: a prior patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention in suit, *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed.Cir. 1983), cert. denied, 469 U.S. 851, 105 S.Ct. 172, 83 L.Ed.2d 107 (1984); elements of separate prior patents cannot be combined when there is no suggestion of such combination anywhere in those patents, *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed.Cir.1984); and a court should avoid hindsight, *W.L. Gore & Associates, Inc.*, 721 F.2d at 1553, 220 USPQ at 313.

8. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 929, 932 (Fed.Cir.1984); *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 771, 218 USPQ 781, 789 (Fed.Cir.1983), cert. denied, 465 U.S. 1026, 104 S.Ct. 1284, 79 L.Ed.2d 687 (1984).

9. See *In re Hall*, 781 F.2d 897, 899, 228 USPQ 453, 455 (Fed.Cir.1986); *Reading & Bates Construction Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 649–50, 223 USPQ 1168, 1171–72 (Fed.Cir.1984). Whether something legally within the prior art is "analogous" is a fact

Failure here to employ established legal standards led to the second set of findings nonprobative and clearly erroneous under Rule 52(a). See Part X.

### Conclusion on Part I

[9] A determination that an invention would have been obvious when it was made to one of ordinary skill in the art under § 103 is thus a conclusion of law based on fact. The "degree to which" it is one of fact is solely that degree required to erect a foundation of facts capable of supporting the conclusion, those facts having been found by applying correct legal standards and expressed in findings free from clear error and based on clear and convincing evidence.

[10] A determination that an invention would not have been obvious when it was made to one of ordinary skill in the art is also a conclusion of law. At trial's outset, that conclusion is in place. See § 282 and Part III. The factual questions are those raised by the patent challenger in an effort to replace the existing with a contrary conclusion, and those, if any, raised by the patentee in rebuttal of the challenger's case.

### Part II

#### Applicability of Rule 52(a) to the § 103 Issue

*Graham, Anderson*,<sup>10</sup> Rule 52(a), and the clearly erroneous standard have, before the remand, been consistently applied by this court in affirming judgments that upheld a patent and judgments that struck

question on "content" of the prior art. See *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 313–14, 227 USPQ 766, 768–69 (Fed.Cir. 1985); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed.Cir. 1983).

10. *Anderson v. City of Bessemer City*, 470 U.S. 564, 574, 105 S.Ct. 1504, 1512, 84 L.Ed.2d 518, 528 (1985) ("Where there are two permissible views of the evidence, the fact finder's choice between them cannot be clearly erroneous.").

down a patent.<sup>11</sup> In the case at bar, our earlier opinion having noted that reversal was required by legal error and the district court's correct and controlling findings on objective evidence of nonobviousness, explicit reference to Rule 52(a) was not made.<sup>12</sup>

[11] Rule 52(a) is applicable to all findings on the four inquiries listed in *Graham*: scope and content of prior art; differences between prior art and claimed invention; level of skill; and objective evidence (secondary considerations). The last may include: commercial success due to the invention; failure of others; long felt need; movement of the skilled in a different direction; skepticism of experts (see *United States v. Adams*, 383 U.S. 39, 52, 86 S.Ct. 708, 714, 15 L.Ed.2d 572, 580, 148 USPQ 479, 484 (1966)); copying the invention in preference to the prior art (see *Diamond Rubber Co. v. Consolidated Rubber*

*Tire Co.*, 220 U.S. 428, 441, 31 S.Ct. 444, 450, 55 L.Ed. 527, 534 (1911)); and other events proved to have actually happened in the real world (hence the description "objective").<sup>13</sup>

Rule 52(a) is thus fully applicable to all findings on which the § 103 issue is decided, but findings must be made on, and the § 103 issue must be decided in light of, all the probative evidence.

### Part III

#### The Statutory Burden of Proof

[12] It is neither necessary nor appropriate for a court to declare a patent valid.<sup>14</sup> A trial court is required by Congress, 35 U.S.C. § 282, *supra* note 1, to say only whether the patent challenger carried its burden of establishing invalidity in the particular case before the court. 774 F.2d at

11. A partial list of pre-April 1986 cases in which this court has applied Rule 52(a), *Graham*, and *Anderson* would include: *Windsurfing International, Inc. v. AMF Inc.*, 782 F.2d 995, 1000, 228 USPQ 562, 566 (Fed.Cir.), *cert. denied*, — U.S. —, 106 S.Ct. 3275, 91 L.Ed.2d 565 (1986); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 313, 227 USPQ 766, 768 (Fed.Cir.1985); *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1573, 224 USPQ 409, 411 (Fed.Cir.1984); *Shelcore, Inc. v. Durham Industries, Inc.*, 745 F.2d 621, 625–26, 223 USPQ 584, 587 (Fed.Cir.1984); *Jervis B. Webb Co. v. Southern Systems, Inc.*, 742 F.2d 1388, 1393, 222 USPQ 943, 946 (Fed.Cir.1984); *Vandenberg v. Dairy Equipment Co.*, 740 F.2d 1560, 1565, 224 USPQ 195, 197 (Fed.Cir.1984); *Radio Steel & Manufacturing Co. v. MTD Products, Inc.*, 731 F.2d 840, 846, 221 USPQ 657, 661–62 (Fed.Cir.), *cert. denied*, 469 U.S. 831, 105 S.Ct. 119, 83 L.Ed.2d 62 (1984); *Seattle Box Co. v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 823, 221 USPQ 568, 572 (Fed.Cir.1984); *Gardner v. TEC Systems, Inc.*, 725 F.2d 1338, 1344–45, 220 USPQ 777, 782–83 (Fed.Cir.) (in banc), *cert. denied*, 469 U.S. 830, 105 S.Ct. 116, 83 L.Ed.2d 60 (1984); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed.Cir. 1983); *Carl Schenck, A.G. v. Nortron*, 713 F.2d 782, 785, 218 USPQ 698, 700 (Fed.Cir.1983).

12. See, e.g., *Pullman-Standard v. Swint*, 456 U.S. 273, 287, 102 S.Ct. 1781, 1789, 72 L.Ed.2d 66, 79 (1982) (findings based on erroneous view of the law may be set aside on that basis alone); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1547, 220 USPQ 303, 308 (Fed.Cir.1983),

*cert. denied*, 469 U.S. 851, 105 S.Ct. 172, 83 L.Ed.2d 107 (1984) ("Where, as here, dispositive legal error occurred in interpretation and application of the patent statute, 35 U.S.C., the parties' arguments relating to the salutary injunction of Fed.Rule Civ.P. 52(a) cannot be controlling on all issues.").

Dennison's brief on appeal correctly said Panduit had to carry its burden on appeal by establishing either legal error or erroneous findings, citing *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1555, 225 USPQ 26, 30 (Fed.Cir.1985).

Dennison's brief also charged the district court with legal error in rejecting Dennison's delay defense. This court affirmed, expressly adding that certain findings were not clearly erroneous. 774 F.2d at 1100, 227 USPQ at 350.

13. Another description: "Circumstantial evidence of the highest probative value." Rich, *Laying the Ghost of the "Invention" Requirement*, in *Nonobviousness—The Ultimate Condition of Patentability* 1:501, 513 (J. Witherspoon ed. 1978). "In appraising an inventor's contribution to the art ... the most reliable test is to look at the situation before and after it appears." *Safety Car Heating & Lighting Co. v. General Electric Co.*, 155 F.2d 937, 939, 69 USPQ 401, 402 (2d Cir.1946) (L. Hand, J.); see also *Graham*, 383 U.S. at 17–18, 86 S.Ct. at 693–94, 15 L.Ed.2d at 556–57, 148 USPQ at 467.

14. *Environmental Designs, Ltd. v. Union Oil Company of California*, 713 F.2d 693, 699 n. 9, 218 USPQ 865, 871 n. 9 (Fed.Cir.1983), *cert. denied*, 464 U.S. 1043, 104 S.Ct. 709, 79 L.Ed.2d 173 (1984).

1096, 227 USPQ at 346. When the burden has not been carried, a court need only so state. When that burden has been carried, the court should declare the patent invalid. The *statute* makes a patent presumptively valid when issued and imposes the burden of establishing invalidity on the challenger.<sup>15</sup> It is the judiciary's duty to follow statutes that requires a trial court lacking a conviction of obviousness to hold that the challenger's burden was not carried.<sup>16</sup> Thereupon, the patent simply remains valid until another challenger carries the § 282 burden.

[13] The presumption mandated by § 282 is applicable to all of the many bases for challenging a patent's validity. When, as here, the sole challenge is an allegation of obviousness, the presumption is that the invention would not have been obvious.

[14, 15] A determination of anticipation under 35 U.S.C. § 102 may be reached by comparing only the claims and a prior art disclosure submitted by the patent challenger. A determination that a patent challenger has not carried its § 282 burden under § 103 may be reached on consideration of only the evidence submitted by the patent challenger. A determination that a patent challenger has carried its burden of establishing obviousness under § 103, however, requires full consideration of any objective evidence of nonobviousness presented in rebuttal. That § 103 issue cannot fairly be decided on only one party's part of the evidence (e.g., patent challenger's prior art), while disregarding the compel-

ling impact of the other party's part (e.g., patentee's objective evidence). Nor is there warrant for singling out § 103 as an area in which courts may disregard the probative force of any part of the evidence.<sup>17</sup>

As noted at 774 F.2d at 1099 n. 24, 227 USPQ at 349 n. 24, patent challenger Dennison told the trial court it should disregard the objective evidence of nonobviousness unless it were "undecided" after viewing only the prior art. Dennison mischaracterized this court's opinion in *W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed.Cir.1983), *cert. denied*, 469 U.S. 851, 105 S.Ct. 172, 83 L.Ed.2d 107 (1984), as support for that misstatement of law. The district court accepted and applied that erroneous legal analysis. Thus the court decided on only part of the evidence, disregarded the controlling impact of its own unchallenged findings on the objective rebuttal evidence of nonobviousness (evidence that may be, as here, the *most* probative), and shifted the statutory burden of proof.

One sued for patent infringement has over twenty possible defenses. Respecting the "would have been obvious" defense, misperceptions in pre-1982 court opinions<sup>18</sup> have led this court to say the judicial process requires that a court withhold a conclusion of obviousness until it has fully assessed the impact of any objective evidence of nonobviousness. Only then can a

15. As this court has said, the presumption of validity is procedural, not substantive, 774 F.2d at 1097, 227 USPQ at 347, but its burden assignment cannot be transferred. The district court here spoke of *plaintiff's* "errors" (reliance on claim limitations and disregard of general principles of physics/common experience) affecting the "plaintiff's case." But plaintiff Panduit, contrary to the impression it apparently itself created, had no "case" or burden to "prove" validity. As explained in this court's opinions in this case, the district court erred in law in its disregard of the claim limitations and in its reliance on principles of physics/experience.

16. "Judicial power is never exercised for the purpose of giving effect to the will of the judge;

always for the purpose of giving effect to the will of the legislature; or, in other words, to the will of the law." *Osborn v. Bank of the United States*, 22 U.S. (9 Wheat.) 738, 866, 6 L.Ed. 204, 234 (1824) (Marshall, C.J.).

17. For a court to disregard the decision-directing impact of any evidence en route to any conclusion on any issue, would be to dim what Coke called the "gladsome light of jurisprudence." COKE, *First Institute: Epilogue*.

18. See, e.g., *Republic Industries, Inc. v. Schlage Lock Co.*, 592 F.2d 963, 975-76, 200 USPQ 769, 782 (7th Cir.1979).

court base its judgment, as it must, on *all* probative evidence of record.<sup>19</sup>

Consideration of all the evidence may or may not require a conclusion that what may appear obvious *to the court*<sup>20</sup> would not have been obvious (because for years it was not) to those of ordinary skill when the invention was made. When a district court has admitted evidence and made findings establishing nonobviousness, disregard of their legal impact is a jurisprudentially improper approach gravely damaging the concepts of fair trial and principled decision-making under the statutes, §§ 103, 282.

This court's many judgments of patent invalidity show that § 282 and a requirement to consider all evidence do not unduly burden patent challengers. Nonobviousness evidence must be weighed along with closeness of the prior art and other evidentiary factors such as nexus with the claimed invention; see for example the discussion in cases in which this court has affirmed a district court's assignment of little weight to objective evidence that was insufficient for varying reasons.<sup>21</sup>

The district court here recognized that the prior art was not close, expressly faulting Panduit for relying on that fact. See *supra* note 15 and 774 F.2d at 1089-90, 227 USPQ at 341. Evaluated under established legal standards, the prior art here was so remote as not to have suggested anything like the claimed inventions to those working for years and at great expense to design a successful cable tie. As discussed in

our earlier opinion, the district court erred in holding to the contrary.

The strong evidence of nonobviousness, and its inescapable refutation of the view that the claimed inventions would have been obvious from the prior art, are what distinguish this case from some others. As the district court said, "This is a case which presents that issue [effect of nonobviousness evidence] as clearly as any I've seen." That evidence, coupled with the remoteness of the prior art, also resolves in this case the "difficulties" seen in *Graham*, 383 U.S. at 18, 86 S.Ct. at 694, 15 L.Ed.2d at 556, 148 USPQ at 467.

[16] According to the uncontroverted evidence, with the prior art before its researchers for years, Dennison conducted a long, expensive research project and produced its "ladder" tie, a tie entirely different from those of the claims in suit. Then, as the court found, Dennison copied Caveney's inventions. When sued, it resurrected that same art for litigation purposes, saying what it copied from Caveney had been obvious to Dennison all along. Even then, knowing from Caveney's patents where it wanted to go at trial, Dennison could only misconstrue the claims and reconstruct the prior art to make it look like what it copied. Dennison's obviousness defense is clearly refuted in this case by the unrefuted record of its own long and frustrating experience and that of others.<sup>22</sup>

19. *Simmons Fastener Corp. v. Illinois Tool Works, Inc.*, 739 F.2d 1573, 1574-75, 222 USPQ 744, 746 (Fed.Cir.1984), *cert. denied*, 471 U.S. 1065, 105 S.Ct. 2138, 85 L.Ed.2d 496 (1985); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39, 218 USPQ 871, 879 (Fed.Cir.1983).

20. At trial, Panduit's counsel quoted the trial court's modest statement in an earlier case: "[I]f I think I might have gotten some clue from this myself, then I know it's obvious to anybody that has anything like ordinary skill." The court responded: "That is the way I tend to feel." In *Stratoflex*, 713 F.2d at 1538, 218 USPQ at 879, this court pointed out that the test under the statute is *not* whether an invention appears obvious "to a judge ... after learning all about the invention."

21. *E.g., Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 315-16, 227 USPQ 766, 770-71

(Fed.Cir.1985); *Cable Electric Products, Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1026-27, 226 USPQ 881, 887-88 (Fed.Cir.1985); *Vandenberg v. Dairy Equipment Co.*, 740 F.2d 1560, 1567, 224 USPQ 195, 199 (Fed.Cir.1984); *Kansas Jack, Inc. v. Kuhn*, 719 F.2d 1144, 1151, 219 USPQ 857, 861 (Fed.Cir.1983). Sufficiency and nexus are clear in the present case.

22. In *Graham*, 383 U.S. at 36, 86 S.Ct. at 703, 15 L.Ed.2d at 566, 148 USPQ at 474, the Court noted "in the circumstances of [that] case" that unsuccessful attempts of others before issuance of the uncited Livingstone patent (showing a device virtually identical to Scoggins'), and failure of others to acquire the knowledge of Livingstone stressed in the Patent and Trademark Office (PTO), could not tip the scales of patentability. Here the scales are tipped, for Caveney alone disclosed his claimed combination, no

Dennison clearly did not carry its § 282 burden of proving that Caveney's claimed inventions would have been obvious under § 103.

#### Part IV

##### *Caveney's Inventions—Effect of His Claims*

The drawings may be deceptive in seeming to show merely a simple, small, plastic tie.<sup>23</sup> The contrary, however, is established by the undisputed record, including the testimony of Dennison's own engineer witnesses quoted at 774 F.2d 1096, 227 USPQ 346, e.g., "a good tie is a damn difficult thing to design, extremely difficult". Caveney's particular claimed cable ties constitute important contributions achieved not easily but only after years of effort and investment of a million research dollars,—and never achieved in years of research by Dennison, whose tie designs did not remotely resemble the claimed ties until it copied them.

It was undisputed that the ties of Caveney's '538 patent, for example, are applied to groups of parallel cables by an installing machine, reliably and safely holding together the many cables in critical environments such as jet airliners. Caveney's contribution to the safety of the airline riding public is a social benefit.

Though technology has burgeoned, the patent system is not limited to sophisticated technologies and powerful corporations. Nowhere in the statute or the Constitution is the patent system opened only to those who make complex inventions difficult for judges to understand and foreclosed to those who make less mysterious inventions a judge can understand after hearing, as here, the inventor's explanation of his invention and the engineering principles he employed. The constitutional pur-

pertinent prior art patent went uncited, the attempts of Panduit, Dennison and others continued right up to the time Caveney made his inventions, and Dennison's engineers had all the prior art patents before them throughout their years of research effort.

pose is to encourage disclosure of patentable contributions to "progress in the useful arts", *all* the useful arts, not just the esoteric. The statute requires utility, novelty, and nonobviousness, not complexity.

That cable ties look alike to a casual observer who sees only straps, heads, and locking elements is not determinative. What is determinative and unchallenged on this record is that those elements were available to workers in the art for years before Caveney made his inventions (and remain available today). In viewing the prior art, the district court improperly treated all cable ties as virtually interchangeable (after hearing all about Caveney's inventions and then viewing the ease with which creative defense counsel reconstructed the prior art at his ease). The fact is clear and unchallenged on the record, however, that the crucial structural distinctions set forth in the claim limitations gave the claimed inventions the distinction that led the industry and Dennison to prefer Caveney's structure over anything in the prior art.

Dennison submitted no tests and no testimony challenging the superiority of the claimed ties found by the district court. Nor did it submit evidence that any prior cable tie suggested Caveney's crucial claimed structural limitations that accounted for the success of his inventions.<sup>24</sup>

The claims are not mere semantic exercises and the present inventions are not insignificant variations or innovations of a commonplace sort. *Graham*, 383 U.S. at 16, 86 S.Ct. at 693, 15 L.Ed.2d at 555, 148 USPQ at 466. The district court found that Caveney achieved and disclosed a "preeminent commercial product" long sought without success by others. Thus Caveney trod well the long and failure-strewn path not only to the Patent Office, *id.* at 19, 86 S.Ct. at 694, 15 L.Ed.2d at 557, 148 USPQ

23. Dennison repeatedly emphasizes what is legally innocuous, i.e., that most cable ties employ straps, heads, and locking elements.

24. Nor did Dennison anywhere suggest a reason, other than their great superiority, for its compulsion to copy Caveney's inventions.

at 467, but to a successful and useful product.

The sole effect of the grant to Caveney of the property right, 35 U.S.C. § 261, to exclude others for a limited time from unauthorized use of his inventions is to require that others avoid the claimed structure newly disclosed to the public in the patent documents. Thus Caveney's claims do not remove existing knowledge from the public domain, for there was no such knowledge until Caveney disclosed it in his patents. Nor do those claims restrict access to materials earlier available, for those materials remain available. Contrary to the misstatement by Dennison to the trial court and to the Supreme Court, *see* Appendix, the patent law is and has always been clear, certain, and immutable that, during the short life of the patents in suit, Dennison and all workers in the art remain perfectly free to employ and combine straps, heads, and pawls as those elements were before the Caveney inventions. They need only avoid Caveney's own novel combination and structure as claimed. *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548, 220 USPQ 193, 198 (Fed.Cir.1983).<sup>25</sup>

[17] Under our economic and patent systems, valuation of the *worth* of an inventor's contribution is left to the public, *not* to the judiciary in determining patentability. A judge is nowhere authorized to declare a patent invalid on his or her personal evaluation. *Graham's* statement, "emphasis on nonobviousness is one of inquiry, not quality," 383 U.S. at 17, 86 S.Ct. at 693, 15 L.Ed.2d at 556, 148 USPQ at 467, can be seen as a recognition that judges are not to decide whether *they* think a

particular invention "ought" to be patented. And that is well. Were it otherwise, a letter to the court would do, and trials, Title 35, and the PTO would be unnecessary.<sup>26</sup>

Though not all inventions achieve public acceptance, many millions in annual sales (\$50 million for Panduit alone), with accompanying taxes and jobs, resulted from Caveney's inventions in the hands of assignee Panduit and admitted copier Dennison. It is undisputed that Caveney's patented ties are novel and useful. The district court found that Caveney's '538 tie leads the industry, and the unchallenged record shows the industry centering on Caveney's inventions, which made owner Panduit No. 1 and copier Dennison No. 2 or 3 in the industry. Caveney's inventions meet the constitutional purpose, for they are classic examples of what the Framers intended when they referred to "Progress of ... useful Arts." U.S.Const. art. I, § 8, cl. 8.

### Part V

#### *This Court's Earlier Opinion—District Court's Approach*

In its earlier Opinion section, this court focused on the law governing obviousness and burden of proof, §§ 103, 282, and on the impact of the district court's uncontestedly<sup>27</sup> correct findings compelling a conclusion of nonobviousness. We expand, somewhat, that focus here.

The law must be the same for all patents and types of inventions. A level playing ground for the marketplace of ideas is as necessary for technological innovation as it

25. In simple truth, Dennison and others had all the prior art elements available for years, and still do, and always will. Dennison was going its own and different way. When Caveney developed "his way," he added to the sum of new and useful knowledge and showed the way to success. Dennison at that point copied Caveney's way and appropriated to itself a large share of his success.

The law is symmetrical. In considering validity and infringement, Caveney's claims must be viewed as drawn to the combination, not to any one element in the combination.

26. *See supra* notes 16 and 20.

27. Dennison's conjectural argument against commercial success is refuted by its own handsome success with its copied product on which all three representative claims read. Dennison also argued that its failed research efforts were due to manufacturing difficulties, yet it experienced none in copying Caveney's ties. In sum, Dennison's arguments are refuted by the record and by the district court's findings.

is for politics and social policy. If the district court's decisional approach in this case were deemed permissible, it would defeat those goals, for it would destroy every patent, frustrate Congress' effort to effectuate its constitutionally granted power and the Framer's intent to promote progress in the useful arts, and disserve the nation's need to encourage research investment. It would also rend asunder the entire body of § 103 law established in this court's precedents since its creation on October 1, 1982.<sup>28</sup>

No effective, uniform, reliable patent system could long survive if the law permitted a decisional approach to § 103 determinations like that here employed by the district court and suggested in Dennison's Petition for Certiorari: (1) interpreting claims by redrafting them to one word; (2) implying that that word describes the "differences"; (3) picking from a prior patent an item describable by that word (in effect finding *no* differences); (4) focusing on isolated minutiae in a prior art patent while disregarding its scope, i.e., its entire disclosure, and how its disclosed structure works; (5) making no finding of a suggestion (because there was no evidence thereof) that items found separately in prior patents could or should be shaped positioned, related, and combined as in the claim; (6) considering as prior art what was not; (7) considering not the problem solved by the invention (here a successful cable tie), but speculating on a "problem" of how prior devices might be reconstructed to match the claimed structure, with the benefit of hindsight aided by the inventor's engineering testimony about the inventions in suit;<sup>29</sup> (8) determining, years later, that an

invention had been obvious all along from the prior art to one of ordinary skill, in the face of a conclusive finding that it had not, and thus would not have, been obvious from that same art to others, including the many highly skilled engineer-cable designers of Panduit and Dennison who had diligently tried and failed for years, at great expense, to design a successful cable tie; (9) disregarding the impact on the § 103 conclusion of the unchallenged finding that others aware of the prior art, including the infringer's cable tie designers, did not find the claimed inventions obvious but were proceeding in directions entirely different from that of the inventor; (10) disregarding the impact on the obviousness conclusion of the unchallenged conclusive evidence that the infringer, with the prior art before it, after years of research (during which, as its own witness said, it was "tantalizingly close," 774 F.2d at 1096, 227 USPQ at 346), and after patenting many of its entirely different "ladder" type ties, did not find the inventions obvious but deemed it necessary to study Caveney's patents and, as the court unequivocally found, "finally came up with" its copy of the inventions; and (11) holding an invention obvious on the basis of "engineering principles" taught the court by the inventor and a subjective view of "common experience" in the face of its own unchallenged finding that the same "principles/experience" did not make that invention obvious to others who, with the prior art before them, went for years in other directions, which others included the highly skilled engineers at Panduit and Dennison who were fully aware of those same principles and who

28. *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 876-77, 228 USPQ 90, 100-01 (Fed.Cir.1985):

The patent system, which is rooted in the United States Constitution (Art. I, § 8, cl. 8), serves a very positive function in our system of competition, i.e., "the encouragement of investment based risk." *Patlex Corp. v. Mas-singhoff*, 758 F.2d 594, 599, 225 USPQ 243, 247, modified on other grounds, 771 F.2d 480, 226 USPQ 985 (Fed.Cir.1985). By so doing, it "encourages innovation and its fruits: new jobs and new industries, new consumer goods and trade benefits." *Paulik v. Rizkalla*, 760

F.2d 1270, 1276, 226 USPQ 224, 228 (Fed.Cir. 1985) (*in banc*).

29. The district court, as did Dennison's expert, used Caveney's patents and his testimony as an instruction book on how to reconstruct the prior art. See Arnold & Nation, *Proving Section 103 Nonobviousness*, in *Nonobviousness—The Ultimate Condition of Patentability* 4:1, 43-44 (J. Witherspoon ed. 1978) (after reading Abraham Lincoln's Gettysburg Address, one may easily re-create it by selecting words from the dictionary).



had even more relevant experience in the art.<sup>30</sup>

Virtually all inventions are necessarily combinations of old elements.<sup>31</sup> The notion, therefore, that combination claims can be declared invalid merely upon finding similar elements in separate prior patents would necessarily destroy virtually all patents and cannot be the law under the statute, § 103.<sup>32</sup>

As explained in our earlier opinion and more fully here, *see* Parts III, IX, the district court's finding that Dennison's effort to carry its § 282 burden with clear and convincing evidence left "room for some difference of opinion," *see* Part IX, should have ended the obviousness inquiry, and, infringement having been conceded, should have resulted in judgment for Panduit. In holding otherwise, the court gave but lip

service to § 282 and effectively transferred the burden of proof fixed by the statute.<sup>33</sup>

## Part VI

### *The Claims Identified*

The parties stipulated that decision on validity of four "representative" claims would be determinative for all. Trial was conducted on only those four claims. Only three of those claims were considered by this court on appeal.<sup>34</sup>

The district court, in "Supplemental Findings and Conclusions" prepared by Dennison, listed 30 claims as "tried to the court." (See the Appendix for Dennison's presentation to the Supreme Court of claim 26, which was listed but was *not* among the four "representative" claims tried to the court and was *not presented to this court.*)

30. Exercise of the hindsight faculty is facilitated when, as here, a party has its expert witness make sketches reconstructing the prior art by inserting as elements of a claim parts selected from separate patents, asks the witness if he finds each of those inserted elements in that sketch, and submits the sketch as evidence. See *Graham*, 383 U.S. at 36, 86 S.Ct. at 703, 15 L.Ed.2d at 566, 148 USPQ at 474, for the value of objective evidence as a guard against hindsight and the temptation to read the inventor's teachings into the prior art.

Further, to deem permissible the approach and theories of counsel described in our earlier opinion would be to resurrect the obfuscation of the law and the resulting nonuniformity and nonreliability in our national law of patents that Congress sought to alleviate when it created this court. See S.Rep. No. 275, 97th Cong. 1st Sess. 3-6, reprinted in 1982 U.S. Code Cong. & Ad. News 11, 13-16.

31. See *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 721 F.2d 1563, 1566, 220 USPQ 97, 99-100 (Fed.Cir.1983); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1540, 218 USPQ 871, 880 (Fed.Cir.1983); *Reiner v. I. Leon Co.*, 285 F.2d 501, 503, 128 USPQ 25, 27 (2d Cir.1960) (L. Hand, J.) ("substantially every invention is for such a 'combination'"); and our earlier opinion, 774 F.2d at 1093, 227 USPQ at 344.

32. We do not imply that Caveney's elements as claimed were all old. On the contrary, the district court did not find, as it could not, that the structural elements as claimed were shown or suggested anywhere in the prior art. See Part IX.

33. Though our earlier judgment has been vacated, our earlier opinion, familiarity with which is presumed, remains in the books. In our earlier opinion: "filed over three months after the '869 patent application" should be deleted from 774 F.2d at 1088, 227 USPQ at 340; "(filed three months after the '538 patent application)" should be deleted from *id.* at 1089, 227 USPQ at 340; "alone" should be inserted before "had", and "the two references pointed to by the district court as disclosing multiple teeth and" should be deleted, in footnote 18, *id.* at 1093, 227 USPQ at 344. None of those errata affects in any way the reasoning or evidentiary and legal considerations on which our earlier reversal was based, and we find no basis for changing any other portion of our earlier opinion. For a full understanding, our earlier and present opinions should be read together.

34. Panduit's appeal dealt with only claim 24 of the '146 patent, claim 6 of the '538 patent, and claim 10 of the '869 patent. Claims must be individually considered. § 282. The numerous nonrepresentative claims were never presented to or discussed by the trial court or this court. Our judgment is necessarily limited to the three claims considered on appeal and included in the appendix at 774 F.2d 1102-04, 227 USPQ 351-52. (Claim 1 of the '538 patent was added because claim 6 includes all limitations of claim 1.) The parties' stipulation does not substitute for a judgment by this court on the nonrepresentative claims.



## Part VII

*Erroneous Claim Interpretations*

[18] In interpreting the claims, the district court committed fundamental legal error when it analyzed each by a single word description of one part of the claimed tie. In patent law, a word ("teeth"; "hinge"; "ledge") means nothing outside the claim and the description in the specification. A disregard of claim limitations, as here, would render claim examination in the PTO meaningless. If, without basis in the record, courts may so rewrite claims, the entire statutory-regulatory structure that governs the drafting, submission, examination, allowance, and enforceability of claims would crumble.

The court's interpretations were doubly contrary to Congress' statutory scheme. First, the claim must particularly point out and distinctly claim the invention. 35 U.S.C. § 112. Second, the "subject matter" that must have been obvious to deny patentability under § 103 is the entirety of the claimed invention, a concept Congress nailed down with the next statutory phrase "as a whole".<sup>35</sup>

[19] When the prior art is compared with erroneously interpreted claims, findings of differences between the prior art and the claims will necessarily be clearly erroneous. When the sole error lies in claim interpretation, a remand for comparison of the prior art with properly interpreted claims is required. Here, however, the error occurred also in: disregard of clear findings of such legal significance as to have left undisturbed the presumption of

nonobviousness that attached when the patents issued; the application under § 103 of erroneous criteria, *see* Parts V, IX; and reliance on prior art so remote from the properly interpreted claims at issue as to preclude a conclusion of obviousness from that art.

[20] The district court erroneously interpreted claim 24 of the '146 patent as drawn only to multiple "teeth":

I conclude that this [claim limitations] is a description of one element, not three.

The district court erroneously interpreted claim 1 of the '538 patent<sup>36</sup> as drawn only to a "hinge":

And that is the essence of '538 patent, the discrete hinge.

The district court erroneously interpreted Claim 10 of the '869 patent as drawn only to a "ledge":

It seems to me, and I so find, that to increase the compressive strength of the cable tie, and specifically the pawl and hinge of the cable tie, you would set the pawl on a ledge.

The district court improperly dismissed the novel structural claim limitations that defined the disposition, positioning, relationship, and operation of the elements in the claims. The ignored claim limitations, however, define crucial structural elements of the invention as a whole, and clearly distinguish (and bind the inventor to the distinction) the whole claimed device from those in prior patents. The prosecution history and the 15 prior patents cited in the PTO establish that no claim was allowed on the mere presence of multiple "teeth",<sup>37</sup> or

35. The concept applies as well to infringement. Dennison did not take one of Caveney's words; it took his whole invention.

36. Claim 6, which includes all limitations of claim 1, was the "representative" claim. The court correctly found that Orban showed a pawl in the as molded position, but erred legally in holding claim 6 invalid on that ground. Claim 6 merely adds a limitation to those in claim 1. It would become meaningful only if claim 1 were invalid and the added limitation were relied on for patentability. That one limitation in claim 6 is shown in a prior patent does not render the entire claim invalid. Because claim

1 is not invalid, the presence of all its limitations in claim 6 preserves the latter's validity.

37. That multiple "teeth" was not "the obvious solution" seen by the district court is further confirmed by the unchallenged documentary record. Before and after Caveney made his '146 invention, other workers in the art designed, and disclosed in their patents, cable ties not only with multiple teeth but with *one-toothed* pawls and locking elements. (*See* Rapata 2,936,980; Emery; Schweser 3,186,047; Geisinger 3,339,246; Orban 3,368,247; Eberhardt 3,484,905; Kahapka 3,542,321; Fay 3,766,608; The Japanese Patent.) Moreover, neither patent

of a "hinge", or of a "ledge". The claims, with their present detailed content, resulted from extensive interaction with the Patent Examiner. The district court pointed to nothing in the prior art that suggested any of the *claimed* constructions.

Interpreted in the light of the specification, claim language, prosecution history, and the other claims, the claims at bar are drawn to entire combinations as set forth at 774 F.2d 1102-04, 227 USPQ 531-52. Each of the numerous limitations of each claim was fully considered in the PTO. If Dennison had avoided in its ties the presence of any *one* limitation in a claim, it would have avoided infringement of that claim. It was a clear error of law for the district court to have ignored the limitations clearly set forth in the claims.

### Part VIII

#### *The Findings In General*

As above indicated, the district court's opinion indicates that it made two sets of findings. It referred to its reality-based first set (clear, fully supported findings on undisputed concrete objective real-world evidence of nonobviousness) not in terms of its operative legal significance, but only in terms of the uncertainty that set created. *See* Part IX. It decided the issue on its speculation-based second set (nonprobative and clearly erroneous findings on prior art modified by Dennison and disputed by Panduit at trial). *See* Part X.

We cannot see why the district court's first set of findings did not require a conclusion that Caveney's inventions, which had for years escaped others who sought them, "would not have been obvious" under § 103; nor why Panduit and Dennison wasted research resources for years if Caveney's inventions were obvious to all throughout those years; nor how the prior

the court cited as showing multiple teeth (Fein or Litwin) involved r suggested their use on a nonreleasabl pawl piv table inside a head having an abutment wall with all of the teeth wedging against that wall.

Had the district court applied the legal standard requiring consideration of the entire prior art as a whole it w uld have noted the correct

art made Caveney's eminently successful inventions obvious to the court in 1984 when it had not made them obvious to skilled engineers (each more skilled than the "ordinary mechanic" referred to in *Hotchkiss v. Greenwood*, 52 U.S. (11 How.) 261, 13 L.Ed. 683 (1851)) who had been designing unsuccessful or far less successful cable ties for years when Caveney's inventions were made in the 1960's.

The district court did deal with the six most relevant patents (all but one were cited by the Patent Examiner). Not one of those patents, however, disclosed a tie remotely approaching the structure or success of the claimed ties. Not one disclosed or suggested all the claimed structural limitations. Not one disclosed or suggested Caveney's claimed combinations. Not one disclosed teeth, a hinge, or a ledge *as claimed*. Nor was there evidence or finding that the patents together suggested the claimed combination.

Though the district court said it "found" the combination obvious, the sole support for that "finding" (sic, conclusion) was the presence in separate prior patents of individual elements differing greatly in shape, position, relation, combination, and function. In relying thereon, the court made a fundamental mistake. A holding of invalidity on that basis, as above indicated, is contrary to statute and would defeat the congressional purpose in enacting Title 35.

Indeed, that the elements noted by the court lay about in the prior art available for years to all skilled workers, without, as the court found, suggesting anything like the claimed inventions, is itself evidence of nonobviousness.

The district court did not follow established legal standards (Part I) in finding the content of the prior art. 774 F.2d at

decisional thrust of its original statement that "others were going in different directions." Noting the different paths foll wed by those skilled in the art, the court w uld not have been as likely to have substituted its wn vi w that "with no prior art at all" th claimed invention "is [sic, would have been] obvi us."

1087-89, 227 USPQ at 339-41. It treated no claim, nor the entire prior art, nor any prior patent "as a whole," but selected bits and pieces from prior patents that might be modified to fit its legally incorrect interpretation of each claim as consisting of one word.<sup>38</sup>

Instead of making express findings on the structural differences as *claimed*, the district court took the *legal* steps of erroneously interpreting: the '146 claim as a one-word (teeth) "solution" to a "problem" (looseness) not disclosed in the Emery patent; the '869 claim as a one-word (ledge) "solution" to a "problem" (compression) not disclosed in any prior patent; and the '538 claim as a one-word (hinge) "solution" to a "problem" (rigidity) it saw in the *nonprior-art* tie of the '869 patent, a tie that *did not exist* when the invention defined in the '538 claim was made.<sup>39</sup>

The court specifically found, *see* Part IX, that Caveney's patents disclosed the best ties in the art. It then spoke of "analogous" items, "expected results" from "ordinary steps," "engineering principles," and "common experience." It nowhere reconciled those evaluations with its contrary findings that no one skilled in the art had for years been led to those evaluations by the prior art. The court's treatment emasculated the crucial, critically important

*structural limitations* that distinguish the claimed inventions from the prior art and that were the key to success of Caveney's inventions.<sup>40</sup>

## Part IX

### *Findings On the Evidence of Nonobviousness*

As recognized by this court and by the Supreme Court in the remand, the district court did articulate much of the correct approach. The court also said "I have done everything I am supposed to do." The court's characterization of its action, and its statement that it knew of the presumption of validity, are not findings and not subject to Rule 52(a).

As noted in our earlier opinion, in any event, the court totally *abandoned* the approach it had articulated. With admirable candor, the court expressed the uncertainty created by the conflict between its conclusion and its clear findings on the evidence of nonobviousness:

Now I want to return to where I started and say that I think Mr. Caveney and Mr. Moody and Panduit have designed and perfected an excellent and, indeed, pre-eminent commercial product, and the fact that they have done so contributed greatly to the difficulty of this case. *It is not*

38. Unlike *Graham*, all prior art patents dealt with here by the court had been cited against one or more of Caveney's patents by the Examiner in the PTO (except the even more remote Japanese patent). The district court said that if it were right and the Examiner wrong, that may be because the Examiner was confused by the eight applications filed by Panduit over two years as listed in DX 60. In 1985, the large examining corps disposed of 128,721 applications, an average of less than two applications per Examiner per week. Commissioner of Patents and Trademarks, 1985 Annual Report 21, 44. The conjecture on Examiner confusion is unwarranted and unsupported. As indicated at 774 F.2d 1094, 227 USPQ 345, the difference between the court and the Examiner in this case lies in adherence by the latter to the statute and legal standards for evaluating prior patents and claimed inventions.

39. The '869 invention was made after the '538 invention. The applications for those patents were filed within a five-day period, but the '869

patent issued first. That and presentation at trial of the '869 patent before the '538 patent appear the basis for the district court's mistake. Though legally improper under § 102, the district court's treatment is of interest on a different plane. When the '869 patent issued, Dennison copied it. PX 12. When the '538 patent issued, over *four years later*, Dennison copied that. PX 13. What the district court saw as obvious in the '538 patent was thus clearly shown not to have been obvious to Dennison's engineers over those four years. It simply makes no sense, under the law or the evidence, to say the '538 invention would have been obvious in light of the '869 patent.

40. In resting its conclusion on speculation about how the skilled *would* employ "engineering principles" and "common experience," in the face of irrefragable proof that they did not for years so employ them, the court approached the area foreclosed by the last sentence of § 103, "Patentability shall not be negated by the manner in which the invention was made."

*easy to find something obvious in the face of those facts. And I do so with great reluctance and great resistance. And in fact I have been going back and forth on this thing in my mind throughout the trial.*

*It gives me great comfort to know that I am just the first stop on this trip. Everything I have said here can be analyzed just as well by the Court of Appeals for the Federal Circuit."*

All the documents are here, the testimony is there for them to read, and if they come to a different conclusion than I, so be it.

This is a case in which the credibility of the witnesses has really played a very small part. It is primarily, it seems to me, a matter of applying your experience to the undisputed facts. It's a matter of interpretation. What do these things teach? *What would they teach* a person of ordinary skill in the art? "

I think there is *room for some difference of opinion* here based largely upon those secondary considerations that have *given me such trouble in this case*: failure by others, copying by Dennison, and unquestioned commercial success of the plaintiff. (Emphasis added.)

In addition, the unchallenged record contains these express statements and findings based on undisputed evidence, not clearly erroneous, and further compelling a conclusion of nonobviousness:

- (1) "Obviously, no previous patent showed the combination at issue here. I am not persuaded that this inven-

41. Despite the district court's invitation to analyze and come to a different conclusion, we do not here merely accept its first set of findings and reject its second set as clearly erroneous. Findings in the second set that this patent disclosed teeth and that disclosed a hinge need not be set aside and may be accepted without effect on the present result, for those findings were legally nonprobative in this case. We hold that the first set so firmly establish nonobviousness in this case as to have precluded the conclusion and judgment based on the second, legally insignificant set. In sum, we hold the district court in its findings "was right the first time."

tion is similar to any one piece of prior art."

- (2) "[O]ther [sic] we were going in different ways and did not arrive at the Caveney structure or anything substantially identical to it."
- (3) "I am satisfied that in plaintiff's patents we see the best of the art at the times in question. The '146 patent [sic, invention] was better than anything else that then existed and the second two patents [sic, inventions], the '869 and '538 patents, were the best at the time."
- (4) "In fact, plaintiff's commercial embodiment of the '538 patent appears to be the leader in the industry."
- (5) "[T]he evidence is simply overwhelming that Dennison copied the '538 patent."
- (6) "And it was only after the issuance of the '538 patent that [Dennison] finally came up with something that looks very much like the '538 patent [sic, tie]."
- (7) "[T]his commercial success, the failure of others, and the copying by Dennison...."

### Part X

#### Nonprobative and Clearly Erroneous Findings

The district court nowhere pointed to anything in the prior art that would have suggested the desirability, and thus the obviousness, of making the distinctive structural elements and combinations Caveney invented and claimed. Nor did the court succeed in the difficult task of cast-

42. Determination of what a patent teaches is fact finding, not interpretation. *Graham*, 383 U.S. at 17, 86 S.Ct. at 693, 15 L.Ed.2d at 556, 148 USPQ at 467. A patent either discloses something or it does not. Moreover, speculation on what prior patents "would" teach is unnecessary in this case, where the trial court unequivocally and correctly found that they had not for many years taught or suggested anything like the claimed inventions to others who were going in other directions.

ing its mind back into that of a person of ordinary skill in the art who had *no preknowledge* of the crucial structural differences that vitalize Caveney's inventions. That person would not have ignored how the devices disclosed in the prior patents worked, or the rigidity of the pawl in Fein, or the releaseability of the pawls in Litwin and the Japanese patents, or the absence of wedging or an abutment wall or anything but air opposing the teeth in Fein and Litwin, or the absence of anything in Emery to suggest a design the court found so much better than what Emery disclosed.

Because the district court's opinion is an admixture of claim mis-interpretation and fact finding without express reference to "differences", it is necessary to glean those portions that may be treated as implied findings on the differences.<sup>43</sup> As above indicated, erroneous claim interpretations led the district court to implied findings that the difference re claim 24 was only multiple teeth in any arrangement, re claim 6 was only a hinge of any type or sort, and re claim 10 was anything that could be called a ledge, but whether a prior patent showed some sort of teeth, or hinge, or ledge, is alone legally insignificant and nonprobative in this case.

Beyond the nonprobative findings, there were these additional "findings", that were clearly erroneous:<sup>44</sup>

#### *The '146 Patent*

"The problem presented by Emery was the so called release problem."

No problem at all is presented in the Emery patent. Like all inventors, Emery presented his invention as flawless. Problems with the Emery tie itself were not seen until years after the patent issued, and, as indicated below, those directly concerned (the distributor and manufacturer

of the Emery tie) saw the problem and its solution as entirely distinct from that envisioned by the court and entirely distinct from Caveney's invention.

"[T]he text of Emery makes abundantly clear that Emery's intention was to achieve wedging against the abutment wall ... inside the head...."

That the Emery patent *as a whole* disclosed to those skilled in the art a pawl that extends outside the head in use is necessarily confirmed by the unchallengeable documentary evidence of the Orban patent, the Bourne patent, and the latter's prosecution history, which together refute defense counsel's argument that Figure 2 was a "draftsman's error."<sup>45</sup>

Two years after the Emery patent issued, the *distributor* of the Emery patent tie filed application for the Orban patent. That application and patent described the problem with the Emery tie as *the cutting off of the chisel edge* (one tooth) when, as was common practice, the protruding strap was cut off. That could happen only if the one tooth were outside the head in use as shown in Figure 2. The distributor's "solution", as Dennison's expert testified, was to raise the end wall of the head.

Four years after the Emery patent issued, the *manufacturer* of the Emery tie further confirmed that the patent as a whole disclosed the pawl outside the head in use. In prosecuting the application filed for the Bourne patent, the manufacturer's attorney told the PTO that the problem with the Emery tie (at even that late date) was "bending of the pawl and tongue [strap] in opposite directions." That could happen only if Emery's pawl was outside the head in use as shown in Figure 2. The manufacturer's "solution" was to keep the pawl inside the head at all times.

43. There are no "findings" on content of the prior art or on "differences" in the Supplemental Findings and Conclusions.

44. It would unduly lengthen this opinion to list every clearly erroneous finding. Because findings of the district court were "clearly erroneous" within the meaning of Rule 52, we "set

them aside". *Icicle Seafoods, Inc. v. Worthington*, — U.S. —, —, 106 S.Ct. 1527, 1530, 89 L.Ed.2d 739, 743 (1986).

45. The Orban and Bourne patents are not prior art to Caveney's '146 patent.

Dennison has not mentioned to us the purpose or function of the serrations (teeth) on the curved surface of Emery's pawl. It was able to get its expert witness to say only that one might *force* the Emery pawl *back* into the head if one applied enough load to bend the end wall, but then it might fall through the head.<sup>46</sup>

"And in order to achieve the parallel kind of relationship between the pawl and the abutment wall that will be necessary for effective wedging, it follows that the teeth of the pawl must be in a straight line and equidistant from the surface of the abutment wall."

The district court learned that effective wedging required a parallel-straightline-equidistant relationship only from Cavey's engineering testimony, and from the hindsight reconstruction of the prior art by Dennison's witness, not from the Emery patent or from any other prior art patent. Dennison, and others the court found were going in different directions, did not learn this from anything in the prior art and the court cited no prior art basis for its statement. As a finding on the prior art, the statement is clearly erroneous.

### *The '538 Patent*

"Now the '869 patent had its own problems."

46. In its Petition for Certiorari, Dennison made much of this court's reference, in footnote 5 of our earlier opinion, to the district court's evaluation of the Emery patent disclosure. Had that footnote controlled our earlier decision, we should have said what is said here, pointing out that the district court's evaluation was contrary to the overwhelming weight of the unchallenged documentary and testimonial evidence, that, though there was evidence to support its evaluation, we were left on the entire evidence with the definite and firm conviction that a mistake had been committed, *United States v. United States Gypsum Co.*, 333 U.S. 364, 395, 68 S.Ct. 525, 541, 92 L.Ed. 746, 765 (1948), and that the evaluation [finding] was therefore "clearly erroneous" under Rule 52(a). Dennison's Petition also quoted a colloquy in which Panduit's counsel said it is possible to read Emery as suggesting wedging against the abutment wall, but that a more reasonable and fair interpretation was one consistent with the drawing. The colloquy

"Now, there are numerous examples in the prior art of hinges and discrete hinges of the kind claimed in the '538 patent. The web in Emery is one example. Litwin has a hinge. Fein, if hinging is a matter of degree, has a hinge, and I refer to Column 2, Line 37 of Fein." "A contemporaneous development that is pertinent is the Bourne patent that had a discrete hinge".

I find nothing in the '538 patent, or at least claim 1 thereof, other than a discrete hinge, that is new over the '869 patent.<sup>47</sup>

This and the court's extended ensuing discussion of the '538 invention in light of '869 "problems" are simply irrelevant. Neither the '869 patent nor the '869 invention *existed* when the '538 invention was made. The '869 invention was the *last* made of all inventions before the court. It is prior art to nothing in the case.

It is clear on the face of Emery, Litwin, Fein, Bourne, and the '146 patent that no hinge remotely "of the kind claimed in the '538 patent" is shown or suggested in the drawings or specifications of any of those patents. On appeal, Dennison made no effort to support this finding. At trial, it abandoned Bourne in view of the PX 77 showing that Bourne disclosed no hinge. Uncontroverted exhibits PX 68, 14D established that Fein disclosed no hinge, despite

is not evidence, and cannot overcome the documentary evidence that those most familiar with the Emery patent tie (and not at the time engaged in this litigation) filed for patents on their own solutions to Emery's "outside the head" pawl long after the Emery patent issued. There are not, therefore, "two permissible views of the evidence" to which this court would apply the injunction of *Anderson v. City of Bessemer City, N.C.*, 470 U.S. 564, 574, 105 S.Ct. 1504, 1512, 84 L.Ed.2d 518, 528 (1985).

47. The '869 invention was not prior art to the invention claimed in the '538 patent, and the '538 invention was not prior art to the invention claimed in the '869 patent. Both inventions were made by the same inventive entity and the applications were copending, having been filed within five days of each other. *In re Land*, 368 F.2d 866, 880, 54 CCPA 806, 825, 151 USPQ 621, 634 (1966). See generally 1 D. Chisum, *Patents*, § 3.08[2] (1986).

its incomprehensible reference to "flexibility pivotable ratchet buckle." It is undisputed that the Emery and '146 hinges were horizontal and in shear. The finding that the prior art disclosed a hinge of the kind claimed is clearly erroneous.

#### *The '869 Patent*

"The problem addressed by that ['869] patent was insufficient strength in compression."

"The Japanese patent and the Litwin patent, which are prior art to the '869 patent, also showed structures analogous to the '869 ledge in that they absorbed compressive force, force exerted by the strap as it was tightened about the bundle."

"But I, nonetheless, find the '869 patent to be obvious both on general principles of physics and in light of the Japanese patent and the Litwin patent."

There is not a word in the '869 patent about compression, or about any "problem" of "insufficient strength," in compression or otherwise. Nor is there a word about absorbing compressive force. The court was here repeating back to Caveney his engineering testimony on the advantages achieved by the structural distinctions in the claim. The court then turned to its legally improper and impossible "general principles" standard of patentability. *See* 774 F.2d at 1097-98, 227 USPQ at 347-48.

The Japanese and Litwin patents disclosed structures entirely distinct from and nonsuggestive of the ledge and pawl structure set forth in claim 10. Both disclosed releasable pawls. Neither disclosed a ledge and pawl inside a frame. Whether those patents showed structures "analogous" because something in them "absorbed compressive force" is irrelevant, claim 10 being drawn to an entirely different *structure*, not to "absorbing compressive force." If the court's discussion be considered an implied finding that the content of the Japanese and Litwin patents constitute disclosures capable of rendering obvious the invention set forth in claim 10, such a finding would be clearly erroneous.

#### CONCLUSION

The portion of the district court's judgment rejecting Dennison's defense under 35 U.S.C. § 102(g) is *affirmed*. The portion of the district court's judgment upholding Dennison's defense under 35 U.S.C. § 103 is *reversed*. The case is *remanded* for further proceedings consistent with this opinion.

**AFFIRMED IN PART, REVERSED IN PART, AND REMANDED**

#### APPENDIX

Dennison's Petition for Certiorari and Reply ignored our earlier opinion's explication of legal error and need to consider all evidence, presented material for the first time, and repeated misstatements of law Dennison employed in the trial court but avoided before this court. This Appendix sets forth the more egregious of the many obfuscating assertions in the Petition and Reply.

"Figure 2, on the other hand, appears to show a pawl which is so long that it cannot fit inside the head." (pp. 4, 5).

That assertion was not made at the trial or on appeal. It appears for the *first time* in the petition.

"And perhaps of greatest significance is the fact that the trial court had before it—although not mentioned in its oral opinion—drawings of the commercial Emery ties and samples of the commercial ties." (p. 7).

"Significance" and Rule 52(a) cannot be applied to what was "not mentioned." No *prior art* "commercial Emery ties" were in evidence. DX 24 (unopened bag of ties surfacing 14 years after Caveney's invention) was handed up at trial and on appeal, but never referred to as prior art. Panduit's brief said, without refutation, that defense counsel *knew* those ties were not prior art.

"The deposition of the U.S. distributor of these ties confirms that the trial court's interpretation of the Emery patent was correct, but the Federal Circuit opinion



## APPENDIX—Continued

simply fails to acknowledge existence of this other evidence." (p. 7).

The deposition was handed to the trial court three minutes before it rendered its oral opinion. It was *not acknowledged* and *not included in the record* by the trial court. The pages of the deposition in the appendix on appeal do not contain the asserted confirmation.

"no invention...." (p. 7); "an invention...." (p. 16); "was invention...." (p. 16); "an invention." (p. 18); "an invention." (p. 20).

See 774 F.2d at 1098, 227 USPQ at 348; *Graham*, 383 U.S. at 14, 86 S.Ct. at 692, 15 L.Ed.2d at 554, 148 USPQ at 465 ("Congress has emphasized 'nonobviousness' as the operative test of the section, rather than the less definite 'invention' language of *Hotchkiss*...."); Rich, *supra* note 13, at 1:508.

"The prior art, as best represented by the Orban patent...." (p. 7).

The district court applied Orban *only* to the dependent portion of claim 6 and *expressly* refused to find Orban relevant to anything else.

"The reference in the '538 drawing to a noncollapsible hinge is incorrect.... Panduit argued in its brief before the Federal Circuit that a 'different embodiment' of its cable ties had the collapsible hinge and the Federal Circuit not only accepted that erroneous statement but then compounded its error by publicly indicting Dennison's counsel for correcting Panduit." (p. 14, n. 3).

The '538 patent repeatedly and only describes the hinge in compression as "rigid, non-collapsible" and the reference in the drawing is therefore *not* "incorrect". Dennison's counsel recognized before the trial court that a collapsible hinge was necessarily a "different embodiment" rejected as "new matter" by the Examiner and Board of Appeals. Dennison is not employing a collapsible hinge and arguing noninfringement.

"'The Obviousness of the Differences'" (p. 17); "'nonobvious differences.'" (p.

19); "'The Obviousness of the Differences'" (p. 8 of Reply).

In *Berkemer v. McCarty*, 468 U.S. 420, 437, 104 S.Ct. 3138, 3149, 82 L.Ed.2d 317, 333 (1984), the Court refused to "accord talismanic power" to a phrase in a prior opinion. To take literally phrases about obviousness of differences themselves would be to place the Court in conflict with the clear language of the statute, § 103, which requires that, *after* the differences are found, the subject matter of the claimed invention be judged *as a whole*. See *Aro Mfg. Co., Inc. v. Convertible Top Replacement Co., Inc.*, 365 U.S. 336, 339, 81 S.Ct. 599, 600, 5 L.Ed.2d 592, 595, 128 USPQ 354, 356-57 (1961) ("the claims made in the patent are the sole measure of the grant."). The differences may render the invention as a whole, as here, so distinct as to produce results of which prior devices are incapable. See *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1546, 221 USPQ 1, 7 (Fed.Cir.1984); *Jones v. Hardy*, 727 F.2d 1524, 1528, 220 USPQ 1021, 1024 (Fed.Cir.1984); *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 721 F.2d 1563, 220 USPQ 97 (Fed.Cir.1983).

"The Federal Circuit's opinion states that the trial court treated the '869 patent as prior art when dealing with the '538 patent. This was another unfortunate departure from the record by the Federal Circuit since explicit contrary statements were made by the trial court.... The trial court's practice does not warrant, we believe, the Federal Circuit's refusal to even acknowledge that supplemental fact findings were made, let alone to suggest that the trial court made misstatements of fact when adopting these supplemental findings. We submit that the Federal Circuit must treat the trial court's supplemental findings as part of the record." (p. 17, n. 5).

Aware of the trial court's legally improper concentration on the '869 patent as though it were prior art, Dennison persuaded the court, a month after its opinion, to list other prior art as "considered" (the list is not a "finding"), carefully excising from the list the '869 patent. This court's



## APPENDIX—Continued

earlier opinion *quoted* the trial court's statement, 774 F.2d at 1089, 227 USPQ at 341, that it found "nothing in the '538 patent ... that is new over the '869 patent." The trial court also said, "the discrete hinge in the '538 patent is not a patentable difference over the '869 patent." The trial court's 14-paragraph discussion leading to the first foregoing quote is entirely based on its view that "the '869 patent had its own problems," that the principal "problem" was insufficient flexibility, and that the cure, "the way the '538 patent does it," was "the so-called discrete hinge." The trial court made *no* "explicit contrary statements" and nowhere said it did *not* rely on the '869 patent as prior art. There was thus no "unfortunate departure from the record," no reason to "acknowledge that supplemental fact findings were made," no refusal to "treat the trial court's supplemental findings as part of the record," and no suggestion "that the trial court made misstatements of fact when adopting these supplemental findings."

"It is apparent that Panduit, Eberhardt, and Bourne all responded at about the same time to the new specifications facing the industry." (p. 20).

"New specifications" were not listed as prior art under § 282 and were not mentioned by the district court. The "Mil Specs" in the record do not require a pawl of any design, and Dennison's entirely different "ladder" ties fully meet those specifications. Dennison's trial brief said Eberhardt sought to avoid pivoting a pawl at its base. Its brief on appeal said Eberhardt's pawl was "pivotally mounted." The trial court said, "It sounds like they [Eberhardt] are claiming the exact opposite kind of virtue from what is claimed in plaintiff's patent." Dennison copied the *claimed* inventions in preference to copying the entirely different "contemporaneous developments" it now praises.

"Dennison faces an injunction and potentially heavy damages if it is ultimately excluded from using such elementary features in its cable ties." (p. 21).

Dennison should know that there is *no possibility in law* for such exclusion. See 774 F.2d at 1093, 227 USPQ 344, and Part VI, *supra*. Dennison knows it is and always will be free to copy the cable ties in the expired prior art patents to Emery, Fein, Litwin, Orban, Eberhart, Bourne, and the Japanese patent, all of which it *praises* as having disclosed all such "elementary features." All Dennison faces is damages for having *copied* Caveney's *claimed* inventions and an injunction against further use of *those* inventions. Even so, Dennison will be free to resume its copying of Caveney's inventions in 1987, 1989, and 1993, respectively.

"comparison of the Emery cable tie with claim 26 of the '146 patent, this claim being one of the 28 claims asserted by Panduit." (p. 2 of Reply.).

Claim 26 was not discussed at trial and was *never presented to this court*.

"Dennison's statements to this Court and to the Federal Circuit were 100% accurate ... more significantly, this petition should be reviewed because of the critical errors made by the Federal Circuit, and not on the basis of such secondary disputes." (p. 10 of Reply).

Dennison's statements were not accurate. See this Appendix and 774 F.2d at 1101-02, 227 USPQ at 350-51. Obfuscation is not merely a "secondary dispute."



(CCPA 1970), as precedent to the contrary since that case concerned a correctly filed reissue application and the subsequent addition of broadened claims. The court simply held that the language "applied for" in the fourth paragraph of 35 U.S.C. § 251 refers to filing of an application for reissue and did not prohibit the addition of broadened claims to the correctly filed application.

The decision of the PTO should be affirmed.



In re John A. DONOHUE.

Serial No. 263900.

Appeal No. 85-868.

United States Court of Appeals,  
Federal Circuit.

July 3, 1985.

Applicant appealed from a decision of the United States Patent and Trade Mark Office Board of Appeals which sustained final rejection of certain claims of an invention relating to acid compounds which were suitable for producing polymers used to form shaped objects such as film, fibers or molded parts. The Court of Appeals, Jack R. Miller, Senior Circuit Judge, held that the claims were properly rejected as anticipated.

Affirmed.

1. Patents ⇨16(2, 3)

Prior art under 35 U.S.C.A. § 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it; such possession is effected if one of ordinary skill in the art could have combined publication's description of the inven-

\* Judge Miller assumed senior status effective

tion with his own knowledge to make the claimed invention.

2. Patents ⇨69

Even if claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling; however, it is not necessary that an invention disclosed in a publication actually be made in order to satisfy the enablement requirement. 35 U.S.C.A. § 102(b).

3. Courts ⇨96(1)

Court of Appeals is bound by decisions of the Court of Customs and Patent Appeals.

4. Patents ⇨72(1)

Anticipation rejection requires a showing that each limitation of a claim must be found in a single reference, practice, or device.

5. Patents ⇨72(1)

Claims of an invention relating to acid compounds which were suitable for producing polymers used to form shaped objects, such as film, fibers or molded parts, were properly rejected under 35 U.S.C.A. § 102(b) as anticipated.

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William Magidson, of Chicago, Ill., argued for appellant.

Harris A. Pitlick, Associate Solicitor, U.S. Patent & Trademark Office, of Arlington, Va., argued for appellee. With him on the brief were Joseph F. Nakamura, Solicitor and John W. Dewhirst, Associate Solicitor, Washington, D.C.

Before MARKEY, Chief Judge, BALDWIN, Circuit Judge, and MILLER,\* Senior Circuit Judge.

JACK R. MILLER, Senior Circuit Judge.

This is an appeal from the decision of the U.S. Patent and Trademark Office ("PTO") Board of Appeals ("board") sustaining the

June 6, 1985.

final rejection of appellant's claims<sup>1</sup> 1, 2, 5, 6, 7, 25, and 28. We affirm.

### BACKGROUND

The subject matter of this appeal was previously before this court's predecessor in *In re Donohue*, 632 F.2d 123, 207 USPQ 196 (CCPA 1980) ("*Donohue I*").<sup>2</sup> There is no need to discuss the details of that opinion; however, a summary of the pertinent facts is appropriate for a full understanding of the issues before us.

The present invention relates to 2,2',6,6'-tetramethylbiphenyl-4,4'-dicarboxylic acid compounds which are suitable for producing polymers used to form shaped objects, such as film, fibers, or molded parts. Claim 1, which is the sole independent claim on appeal, is illustrative:

2,2',6,6'-tetramethylbiphenyl-4,4'-dicarboxylic acid compound comprising said acid, an acyl halide derivative thereof, or a simple ester thereof.

The PTO has rejected all the appealed claims under 35 U.S.C. § 102(b) "as anticipated by Nomura [et al.], optionally in view of Lincoln and Walker [et al.]."

Nomura et al. ("*Nomura*")<sup>3</sup> discloses twelve 2,2',6,6'-tetramethylbiphenyls ("*TMBP*") which are 4,4'-disubstituted with NH<sub>2</sub>, NMe<sub>2</sub>, OH, OMe, Cl, Br, I, CO<sub>2</sub>H, CO<sub>2</sub>Me, CN, NO<sub>2</sub>, or H substituents. Methods of preparing all these compounds, except those disubstituted with CO<sub>2</sub>H or CO<sub>2</sub>Me, are set forth in Nomura. Nomura's disclosure of how to make 4,4'-dinitrile (or dicyano) TMBP is particularly signifi-

cant, because Lincoln<sup>4</sup> and Wagner et al. ("*Wagner*")<sup>5</sup> teach, generally, the preparation of carboxylic acids from nitriles by hydrolysis.

In *Donohue I*, a majority of the Court of Customs and Patent Appeals ("CCPA") affirmed the PTO's rejection of appealed claims 1, 5, 6, and 7<sup>6</sup> under 35 U.S.C. § 102(b). *Id.* at 127, 207 USPQ at 200. The basis for the rejection was, as it is here, Nomura with reference to Lincoln and Wagner. *Id.* at 126, 207 USPQ at 199.

A minority of the CCPA voted to reverse the PTO's decision, because they concluded it was uncertain from the text of Nomura that the dicarboxylic acid TMBP and dimethyl ester TMBP were ever prepared. *Id.* at 129, 207 USPQ at 201. Accordingly, Nomura's disclosure was, in the minority's view, no more than a mere naming of the claimed compounds which is insufficient to constitute an enabling disclosure. *Id.* at 129, 207 USPQ at 201.

After *Donohue I*, the presently-appealed application was filed. During prosecution before the PTO, appellant submitted an affidavit under 37 C.F.R. § 1.132 executed by Dr. Ellis K. Fields ("*Fields affidavit*"). In this affidavit, Dr. Fields states that he wrote to Dr. Yoshito Takeuchi, one of the authors of Nomura, to ask whether the disclosed dicarboxylic acid TMBP or dimethyl ester TMBP compounds were ever synthesized, as indicated in Nomura. Dr. Takeuchi responded by stating that these compounds were not synthesized, and Dr.

1. In application Serial No. 263,900, filed May 15, 1981, for Tetramethylbiphenylcarboxylic Acids and Derivatives Thereof, which is a division of Serial No. 60,909, filed July 26, 1979, and a continuation of Serial No. 622,649, filed October 15, 1975, which is a continuation-in-part of Serial No. 517,506, filed October 24, 1974.

2. *Donohue I* involved application No. 622,649. See note 1, *supra*.

3. Yujiro Nomura and Yoshito Takeuchi, "Substituent Effects in Aromatic Proton Nuclear Magnetic Resonance Spectra. Part VI. [<sup>2</sup>H<sub>6</sub>] Benzene-induced Solvent Shifts in 4,4'-Disubstituted 2,2',6,6'-Tetramethylbiphenyls and Related Compounds," *J. Chem. Soc'y (B)*, 956-60 (1970).

4. U.S. Patent No. 3,876,691, issued April 8, 1975, on application No. 351,696, filed April 16, 1973, for a "Process for the Hydrolysis of Nitriles."

5. Wagner et al., *Synthetic Organic Chemistry* 412-15 (John Wiley & Sons, N.Y., N.Y.) (1965).

6. Claim 1 in *Donohue I* differs from claim 1 of the present appeal only in that the latter includes the limitation "comprising said acid, an acyl halide derivative thereof, or a simple ester thereof." Claims 5, 6, and 7 of *Donohue I* specify the same dependent features as in the presently-appealed claims of the same number.

Fields submitted his affidavit to that effect.

Despite the Fields affidavit, the examiner finally rejected the claims, and an appeal to the board was filed. The board affirmed the rejection of the claims on the grounds stated *supra*, holding that it was bound by *Donohue I*. As to the Fields affidavit, the board held that whether the authors of Nomura actually prepared the claimed compounds is not "material or relevant"; rather, the key factor in evaluating the adequacy of a reference's disclosure was deemed to be whether that disclosure would have been enabling, and the board determined that the CCPA had decided that question with respect to Nomura.

### ANALYSIS

Appellant has made a record different from that in *Donohue I* by submitting the Fields affidavit. This new record presents a new issue of patentability with respect to whether the previously-sustained anticipation rejection can still be maintained. In view of this new issue, the PTO properly declined to make a formal *res judicata* rejection and addressed the question of whether the Fields affidavit overcomes the rejection of the claims based on Nomura. See *In re Ackermann*, 444 F.2d 1172, 1176, 170 USPQ 340, 343 (CCPA 1971); *In re Russell*, 439 F.2d 1228, 1230, 169 USPQ 426, 428 (CCPA 1971); *In re Herr*, 377 F.2d 610, 611, 153 USPQ 548, 549 (CCPA 1967).

Appellant argues that the Fields affidavit, which states that the authors of Nomura did not make the disclosed dicarboxylic acid TMBP and dimethyl ester TMBP compounds, overcomes the PTO's rejection. It is urged that *Donohue I* and *In re Samour*, 571 F.2d 559, 197 USPQ 1 (CCPA 1978), require, *inter alia*, that a 35 U.S.C. § 102(b) rejection based on a primary reference disclosing a claimed compound in conjunction with one or more references which teach how to make that compound, should be sustained only if the claimed compound was actually made. We disagree.

[1.2] It is well settled that prior art under 35 U.S.C. § 102(v) must sufficiently describe the claimed invention to have placed the public in possession of it.<sup>7</sup> *In re Sasse*, 629 F.2d 675, 681, 207 USPQ 107, 111 (CCPA 1980); *In re Samour*, 571 F.2d at 562, 197 USPQ at 4; see also *Reading & Bates Construction Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 651-52, 223 USPQ 1168, 1173 (Fed.Cir.1984). Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention. See *In re LeGrice*, 301 F.2d at 939, 133 USPQ at 373-74. Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. *In re Borst*, 345 F.2d 851, 855, 145 USPQ 554, 557 (CCPA 1965), *cert. denied*, 382 U.S. 973, 86 S.Ct. 537, 15 L.Ed.2d 465 (1966). It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.

*In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1973) and *In re Sheppard*, 339 F.2d 238, 144 USPQ 42 (CCPA 1964), do not support a contrary view. In those cases, the references were deemed insufficient, because they stated that attempts to prepare the claimed compounds were unsuccessful. Such failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling. By contrast, the fact that the author of a publication did not attempt to make his disclosed invention does not indicate one way or the other whether the publication would have been enabling.

Although *In re Samour* and *Donohue I* mention that the claimed invention in each case was apparently produced in conjunction with the anticipatory reference, this is a far cry from proclaiming that such pro-

7. This rule is based on the "described in a printed publication" language in 35 U.S.C. § 102(b).

See *In re LeGrice*, 301 F.2d 929, 936, 133 USPQ 365, 371 (CCPA 1962).

duction is required to meet the enablement requirement. *In re Samour*, in fact, states:

[W]hether or not [the claimed invention] has been made previously is not essential to a determination that a method of preparing it would have been known by, or would have been obvious to, one of ordinary skill in the art.

571 F.2d at 563 n. 6, 197 USPQ at 4 n. 6. Therefore, the statements in *In re Samour* and *Donohue I* that the claimed invention was made previously serve to point out the absence of any strong evidence of nonenablement as in *Wiggins* and *Sheppard*. See *In re Donohue*, 632 F.2d at 126 n. 6, 207 USPQ at 199 n. 6.

[3] At oral argument, appellant also challenged the correctness of the CCPA's holding in *In re Samour* and *Donohue I* that several references can be used together to support an anticipation rejection. However, we are bound by the CCPA's decision in those cases. *South Corp. v. United States*, 690 F.2d 1368, 1370-71, 215 USPQ 657, 658 (Fed.Cir.1982) (in banc). At the same time, we have no difficulty with the rejections made in *In re Samour* and *Donohue I*.

[4, 5] It is elementary that an anticipation rejection requires a showing that each limitation of a claim must be found in a single reference, practice, or device. *E.g.*, *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 771, 218 USPQ 781, 789 (Fed.Cir. 1983), *cert. denied*, — U.S. —, 104 S.Ct. 1284, 79 L.Ed.2d 687 (1984). The anticipation rejection used here, as in *In re Samour* and *Donohue I*, is not inconsistent with this rule. See *In re Marshall*, 578

F.2d 301, 304, 198 USPQ 344, 346 (CCPA 1978). The additional references utilized in this case (viz., Lincoln and Wagner) are not relied upon for suggestion or motivation to combine teachings to meet the claim limitations, as in rejections under 35 U.S.C. § 103. *In re Samour*, 571 F.2d at 563, 197 USPQ at 4-5. Such reliance would be pointless, because Nomura alone discloses every element claimed. The purpose of citing Lincoln and Wagner is, instead, to show that the claimed subject matter, as disclosed in Nomura, was in the public's possession. *Id.* Therefore, the anticipation rejection based on Nomura, Lincoln, and Wagner is proper.<sup>8</sup>

Appellant also argues that the references fail to teach the solubility characteristics and melting point range set forth in dependent claims 25 and 28, respectively.<sup>9</sup> However, where, as here, the dicarboxylic acid TMBP and dimethyl ester TMBP of Nomura are identical to the claimed invention, the properties of Nomura's compounds are inherently the same as those of the claimed invention in the absence of proof to the contrary. See *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977).

In view of the foregoing, the board's decision is affirmed.

AFFIRMED



8. Compare *Studiengesellschaft Kohle, M.B.H. v. Dart Industries, Inc.*, 726 F.2d 724, 220 USPQ 841 (Fed.Cir.1984) (recognized exception occasionally permitting use of additional references in anticipation rejections but holding exception did not apply).

9. Claims 25 and 28 read as follows:

25. The acid of Claim 2, said acid being soluble in ether and N-methyl-2-pyrrolidone.

28. The dimethyl ester of Claim 7, having a melting point of 128-129°C.

are to some extent sold to the same classes of purchasers or advertised in the same publications"—a finding not questioned by the majority. Both the Board and the majority agree that the applicant's broad designation of the goods as power supplies "comprehends static and transistorized power equipment of the character sold by opposer." In other words, regardless of the precise types of equipment now being sold, if registration is allowed, the trademarks may be used in connection with identical goods.

We are not here concerned with the law of unfair competition nor with the right of the applicant to the use of its corporate name, nor with its good faith in adopting it as a trademark. The issue is confusing similarity of the marks and nothing else. It is true that precedents are not very helpful in determining that issue. Even so, I do not see how the court can be applying consistent standards as to likelihood of confusion when it decides that "Dyanshine" and "Disshine" (Barton Mfg. Co. v. Hercules Powder Co., *supra*) are confusingly similar and also that "Winco" and "Wiancko" are not.

This court, in a recent case in which it was held that "Huvilon" so resembled "Uvinul" as to be confusingly similar, pointed out that "The fact that neither name has any meaning apart from the goods on which they are used makes it difficult for a purchaser to keep the names clear of possible confusion based on \* \* similarities." General Aniline & Film Corp. v. Hukill Chemical Corp., Cust. & Pat.App., 287 F.2d 926, 927. In the present case we have two perfectly meaningless words, both of them unusual and neither remotely suggestive of any English word. In the case of ordinary well known English words, most literate people know how the word should be spelled and, therefore, quickly notice a very slight variance. Not so with words like those before us or like "Huvilon" and "Uvinul". It seems to me that the soundness of the court's observation in the "Huvilon" case quoted above is demonstrated by the fact that in a period of seven months the let-

ters received by the applicant showed over 100 different variations or misspellings of its name although the writers had the correct address and thus appeared to be acquainted with the applicant.

I would reverse the decision of the Board.



49 CCPA

**Application of Edward Burton LeGRICE.**

**Patent Appeals Nos. 6727, 6728.**

United States Court of Customs  
and Patent Appeals.

May 4, 1962.

Rehearing Denied July 11, 1962.

Proceeding on applications for patents for *rosa floribunda* plants. The Board of Appeals of the United States Patent Office affirmed final rejection of applications Nos. 709,127 and 709,128, and the applicant appealed. The Court of Customs and Patent Appeals, Smith, J., held that descriptions in foreign publications were not enabling descriptions which could constitute bar to patentability of applications.

Reversed.

# 1. Patents ⇐70

Congress, by enacting no exception with respect to patents for plants, to statute making unpatentable inventions described in printed publications more than one year prior to date of application for patent intended that it be interpreted the same for plant patents as it had been interpreted in relation to patents for other inventions. 35 U.S.C.A. §§ 102 (b), 161.

# 2. Patents ⇐69

Patented inventions cannot be superseded by mere introduction of foreign publication of kind, though of prior date, unless description and drawings contain

and exhibit substantial representation of patented improvement, in such full, clear, and exact terms as to enable any persons skilled in the art or science to which it appertains to make, construct, and practice invention to same practical extent as they would be enabled to do if mere information was derived from prior patent. 35 U.S.C.A. §§ 102(b), 161.

### 3. Patents ⇐69

Before any publication can amount to statutory bar to grant of patent, its disclosure must be such that skilled artisan could take its teachings in combination with his own knowledge of particular art and possess invention. 35 U.S.C.A. §§ 102(b), 161.

### 4. Patents ⇐69

Descriptions in printed publications of new plant variety, to bar patent thereon, must meet requirements of enabling descriptions which in fact place invention in possession of public. 35 U.S.C.A. § 102(b).

### 5. Patents ⇐69

Descriptions in foreign publications were not enabling descriptions which could constitute bar to patentability of applications for patents for *rosa floribunda* plants.

John H. Leonard, Cleveland, Ohio (Spencer B. Michael, Smith, Michael & Gardiner, Washington, D. C., of counsel), for appellant.

Clarence W. Moore, Washington, D. C. (Joseph Schimmel, Washington, D. C., of counsel), for the Commission of Patents.

\* United States Senior District Judge for the Eastern District of Pennsylvania, designated to participate in place of Judge O'Connell, pursuant to provisions of Section 294(d), Title 28, United States Code.

#### 1. Sec. 161. Patents for plants

Whoever invents or discovers and asexually reproduces any distinct and new variety of plant, including cultivated sports, mutants, hybrids, and newly found seedlings, other than a tuber propagated plant or a plant found in an uncultivated

Before WORLEY, Chief Judge, and RICH, MARTIN, and SMITH, Judges, and Judge WILLIAM H. KIRKPATRICK.\*

SMITH, Judge.

The issue on these consolidated appeals is whether appellant is entitled under 35 U.S.C. 161<sup>1</sup> to a patent on each of his applications serial numbers 709,127 and 709,128, filed January 15, 1958, each entitled "*Rosa Floribunda Plant*." The Patent Office Board of Appeals affirmed the final rejection of both applications under 35 U.S.C. § 102(b) on the ground that the inventions had been described in printed publications in England more than one year prior to the dates of filing of the said applications. The publications occur in the National Rose Society Annual of England and in catalogues. The Annual describes appellant as having raised the roses described and the catalogues show color pictures of these roses. There is no dispute that the publications relate to and picture the identical roses which were originated by appellant and which he now seeks to patent.

Resolution of the issue on these appeals requires us to determine whether as a matter of law, the English publications constitute, within the meaning of 35 U.S.C. § 102(b), a bar to appellant's right to patents on said applications.

The applicable portion of 35 U.S.C. § 102(b) reads:

"A person shall be entitled to a patent unless— \* \* \* (b) the invention was \* \* \* described in a printed publication \* \* \* more than one year prior to the date of the application for patent in the United States, \* \* \*."<sup>2</sup>

state, may obtain a patent therefor, subject to the conditions and requirements of this title.

The provisions of this title relating to patents for inventions shall apply to patents for plants, except as otherwise provided. (July 19, 1952, ch. 950, 66 Stat. 804; Sept. 3, 1954, c. 1259, 68 Stat. 1190.)

2. This section is derived from 35 U.S.C. (1940 ed.) 31, R.S. 4886, Act of Mar. 3, 1897, c. 391, which was derived from Act

Thus, the statute expressly prohibits the granting of a patent on an invention or discovery which has been "described in a printed publication \* \* \* more than one year prior to the date of the application for patent in the United States." Long prior to the inclusion of this provision in 35 U.S.C. § 102(b), the courts had construed earlier provisions and had interpreted them with regard to what must be described in a printed publication in order for the publication to be a bar to the grant of a patent. The underlying concept on which the courts permitted such a bar is that the description of the invention in the printed publication was sufficient to give possession of the invention to the public.

The express provision of 35 U.S.C. § 161 permits the granting of patents on the particular classes of plants therein enunciated which include "Rosa Floribunda Plants" disclosed in the applications on appeal. Grant of such a patent is, however, "subject to the conditions and requirements" of Title 35 "except as otherwise provided." Thus, appellant's right to patents on his applications is subject to the bar stated in 35 U.S.C. § 102(b), if the publications in issue meet the legal requirements necessary to establish such a bar.

The particular question of law to be here decided is presented on stipulated facts which, insofar as they relate to the issue, are here quoted from the record:

"4. Each application was accompanied by the conventional formal oath containing the statement that the applicant did not believe the variety of plant was described in any printed publication in any country more than one year prior to his application, but adding the following additional recitations:

"(a) In Serial No. 709,127,— [Charming Maid] 'that certain information relative to the new variety was published in the National Rose

Society Annual, of England, for 1954 on pages 156 and 157 and like information was published more than one year prior to the date hereof in catalogues, but he believes that such information cannot enable anyone to practice the invention by producing the present variety.'; and

"(b) In Serial No. 709,128,— [Dusky Maiden] 'that certain information relative to a new variety was published in the National Rose Society Annual, of England, in 1949 on page 155, and like information was published more than one year prior to the date hereof in catalogues, but he believes that such information cannot enable anyone to practice the invention by producing the variety'.

"5. (a) The disclosures in the Rose Annual of 1949, page 155, insofar as pertinent, is [sic] as follows:

"The Gold Medal Award was made to:—(Here follows the list of roses, including Dusky Maiden)—

"—Dusky Maiden (Hy. Poly.) raised and exhibited by E. B. LeGrice, North Walsham.—Glowing dark scarlet with dusky velvety sheen. Single blooms carried in large trusses. Size when open 3-in. in diameter. Very fragrant. Vigorous. Foliage dark green and abundant. Bedding. Trial Ground Certificate, 1945. Prune 34.'

"(b) The disclosure in the Rose Annual of 1954, pages 156 and 157, is as follows:

"The Trial Ground

"List of Trial Ground Awards, 1953

"(To which is appended the Show Awards in 1953.)

"(Here follows a list of roses, including Charming Maid)—

"—Charming Maid (Flor.). Trial Ground No. 624. Reg. No. 269. Dainty Maiden x Mrs. Sam McGredy.



Raiser and Distributor E. B. Le-Grice, North Walsham. Vigorous growing variety with deep glossy green foliage 16. Freedom from disease 16. Large single flowers borne in small clusters. Colour pink shaded gold 16. Freedom of flowering 16. General effect 6. Fragrance 5. Gold Medal Provincial Show, 1953.'

"6. In each case, the prior catalogue publication referred to in the oath includes a color picture of the rose clear enough to establish identity in appearance between the rose illustrated and the applicant's variety, and the catalogue publication with the picture establishes that the rose described and illustrated is the variety described and claimed in the application, and the rose so described and illustrated is, in fact, the variety so described and claimed in the application."

The unique aspects of plants which are the subject of plant patents have posed numerous problems to various tribunals charged with the application of basic patent law concepts thereto. A review of all the reported decisions dealing with plant patents<sup>3</sup> establishes that the present case presents a legal problem of first impression on which there are no controlling precedents.

35 U.S.C. § 161 is based on an amendment, effective May 23, 1930, to R.S. 4836, (Sec. 31 of former title 35 U.S.C.), which originated in House Bill 11372 of the Second Session of the 71st Congress. The Committee on Patents which reported the bill filed a report stating:

"The purpose of the bill is to afford agriculture, so far as practicable, the

same opportunity to participate in the benefits of the patent system as has been given industry, and thus assist in placing agriculture on a basis of economic equality with industry. The bill will remove the existing discrimination between plant developers and industrial inventors. \* \* \*

The report expresses the hope that the bill "will afford a sound basis for investing capital in plant breeding and consequently stimulate plant development through private funds". It then goes on to state:

"No one has advanced a just and logical reason why reward for service to the public should be extended to the inventor of a mechanical toy and denied to the genius whose patience, foresight, and effort have given a valuable new variety of fruit or other plant to mankind.

"This bill is intended not only to correct such discrimination, but in doing so it is hoped the genius of young agriculturists of America will be enlisted in a profitable work of invention and discovery of new plants that will revolutionize agriculture as inventions in steam, electricity, and chemistry have revolutionized those fields and advanced our civilization."

An identical report was filed by the Senate Committee on Patents.

The unique nature of a plant patent was recognized by the Patent Office Board of Interference Examiners in *Dunn v. Ragin v. Carlile*, 50 USPQ 472 (1941) where at p. 474 it was recognized "The mere filing of an application for a patent

3. Sugar Cane—*Bourne v. Jones*, D.C., 114 F.Supp. 413.

Dream Navel Orange—*Nicholson v. Bailey*, D.C., 182 F.Supp. 509.

Nectarine—*Kim Bros. v. Hagler*, D.C., 167 F.Supp. 665.

Roses—*Armstrong Nurseries, Inc. v. Smith et al.*; *Same v. Hood et al.*; *The Conard-Pyle Company v. Smith et al.*; *Jackson & Perkins Company v. Smith et al.*; *Same v. Hood et al.*, D.C., 170 F. Supp. 519.

Upright Barberry—*Cole Nursery Co. v. Youdath Perennial Gardens, Inc. et al.*, D.C., 17 F.Supp. 159.

Bacteria—*In re Arzberger*, 112 F.2d 834, 27 CCPA 1315.

Pineapple Orange—*Dunn v. Ragin v. Carlile*, 50 USPQ 472.

Syngonium Plant—*Ex Parte Foster*, 90 USPQ 16.

Peach Tree—*Ex Parte Moore*, 115 USPQ 145.

for a new variety of plant would not enable anyone to reproduce such a plant."

35 U.S.C. § 161 engrafts the Plant Patent Act onto the basic patent law, which requires us to apply thereto all the rules, regulations and provisions of the basic patent law except that, by the express provision of 35 U.S.C. § 162, a plant patent cannot be declared invalid if its description "is as complete as is reasonably possible."

As indicated by the Committee reports and as provided in the statutory provisions, the law of plant patents is so inextricably bound up with the earlier general patent law that the former cannot be understood without consideration of the latter, and as provided in 35 U.S.C. § 161, the provisions of Title 35 "relating to patents for inventions shall apply to patents for plants, except as otherwise provided."

It appears, therefore, to have been the intent of Congress that plant patents and patents for other inventions should be subject to the same statutory provisions "except as otherwise provided."

[1] Thus in determining the meaning of 35 U.S.C. § 102(b) as it applies to patents for plants, the first consideration is that Congress did not provide any exception thereto, so it should be presumed that Congress intended that it should be applied to patents for plants as it had been previously applied to patents for other inventions. In other words, we think Congress, by enacting no exception to 35 U.S.C. § 102(b) with respect to patents for plants, intended that it be interpreted the same for plant patents as it has been interpreted in relation to patents for other inventions. Otherwise a "discrimination" would continue to exist "between plant developers and industrial inventors," which, as indicated in the Committee Reports, Congress intended to eliminate by passage of the Plant Patent provisions.

Since there has been no interpretation of 35 U.S.C. § 102(b) as applied to plant patents, we turn to the prior decisions dealing with its application to patents

on other inventions. In these decisions, we find 35 U.S.C. § 102(b) and its predecessor statutes have been interpreted as requiring that the description of the invention in the publication "must be sufficient to put the public in possession of the invention." Curtis on Patents, 3rd ed., Sec. 378; Seymour v. Osborne, 11 Wall. 516, 555, 20 L.Ed. 33.

Robinson on Patents, Sec. 325, entitled "Prior Publication: its Essential Requisites," summarizes the long recognized requirements of a "Prior Publication" as follows:

"The second method recognized by law in which an earlier invention may be made accessible to the public is by Prior Publication. To have this effect the publication must be: (1) A work of public character, intended for general use; (2) Within reach of the public; (3) Published before the date of the later invention; (4) A description of the same complete and operative art or instrument; and (5) So precise and so particular that any person skilled in the art to which the invention belongs can construct and operate it without experiments and without further exercise of inventive skill. Unless a publication possesses all these characteristics it does not place the invention in the possession of the public, nor defeat the claim of its inventor to a patent."

It is Robinson's 5th characteristic of a prior publication with which we are here concerned. This characteristic is further elaborated in Sec. 330 of Robinson on Patents entitled "Prior Publication: Publication Must Fully Communicate the Invention to the public," which states the rule as follows:

"Finally, the description must place the invention in the possession of the public as fully as if the art or instrument itself had been practically and publicly employed. In order to accomplish this, it must be so particular and definite that *from it alone, without experiment or the exertion of his own inventive skill,*

any person versed in the art to which it appertains could construct and use it." [Emphasis ours.]

Walker on Patents, Deller Edition at p. 271, states:

"And a claim for an article of manufacture may be anticipated by a prior patent or printed publication, which describes the article, without describing any process of making it; *provided a knowledge of the article would teach a skillful mechanic some process of making it.*" [Emphasis ours.]

The underlying public purpose of the patent law, recognized by Congress in enacting the plant patent provisions, is to add to the public store of useful knowledge. This concept is more fully stated in Sec. 36, Robinson on Patents, as follows:

"To stimulate inventive skill and energy is one of the most effective methods of advancing national prosperity, and in modern times especially attracts the attention of all enlightened governments. While it is certain that the human mind, independently of external impulses, is constantly engaged in pushing its investigations into new fields and in achieving new results, it by no means follows that practical inventions in the industrial arts would rapidly be multiplied without the inducement offered by the prospect of pecuniary reward. Such inventions necessitate not only the conception of a new idea by the mind, but the reduction of that idea to practice in some tangible and useful form. This latter process cannot be accomplished by speculation only, but involves experiments, often protracted and expensive, and a degree of physical skill and labor which otherwise applied might secure to the inventor a considerable recompense in money. To lead an able and prudent man to engage in such enterprises as these, some reasonable hope of profiting by his own labors must be aroused with-

in him; and this can be effected only by a promise on the part of the public that if he succeeds in his invention he shall be suitably rewarded. Experience teaches that this is true; the progress of inventive triumphs, in all civilized nations, being directly in proportion to the encouragement offered to inventors by the state."

As pointed out in the Committee Reports, supra, prior to passage of the plant patent provisions, plant breeding and research was dependent, in large part, upon Government funds to Government experiment stations, or to the limited efforts of the amateur breeder. The Committee Report expresses the hope that the bill "will afford a sound basis for investing capital in plant breeding and consequently stimulate plant development through private funds." The Committee Report then continues:

"In addition, the breeder to-day must make excessive charges for specimens of the new variety disposed of by him at the start in order to avail himself of his only opportunity for financial reimbursement. Under the bill the breeder may give the public immediate advantage of the new varieties at a low price with the knowledge that the success of the variety will enable him to recompense himself through wide public distribution by him during the life of the patent. The farmers and general public that buy plants will be able promptly to obtain new improved plants at a more moderate cost."

The way in which a plant patent advances the public purpose and achieves the result which Congress appears to have intended is stated in Appellant's brief as follows:

"A plant patent performs its function by making it profitable to the developer to make as wide a distribution as possible of the res, the plant itself. If the variety is deserving, hundreds of specimens are likely to

be widely distributed, thereby reducing the danger of their perishing in a common disaster. The likelihood of extinction of the res before an improved variety or worthy successor is developed is thus rendered remote. Publicity informs the public where specimens exist. This is how a plant patent adds to the store of *useful knowledge*."

Before passing to an analysis of the case law with respect to the meaning of "described in a printed publication," as this term is used in 35 U.S.C. § 102(b), it must be borne in mind that there are inherent differences between plants and manufactured articles. Should a plant variety become extinct one cannot deliberately produce a duplicate even though its ancestry and the techniques of cross-pollination be known. Manufactured articles, processes, and chemical compositions when disclosed are, however, susceptible to man-made duplication.

Appellant in his brief points out:

"The description of a plant in a plant patent or in a printed publication at best can only recite, as historical facts, that at one time a certain plant existed, was discovered in a certain manner, and was asexually reproduced. This information may be interesting history, but cannot enable others to reproduce the plant. \* \* \* Prior public use and sale of a plant are the avenues by which a plant enters the public domain."

In the case of manufactured articles, processes and chemical compositions, a different situation prevails. Written descriptions and drawings in publications can often enable others to manufacture the article, practice the process or produce the chemical composition. Thus, with respect to publications in these fields, there is a valid basis in public policy for 35 U.S.C. § 102(b) which bars the granting of patents on inventions "described in a printed publication in this or a foreign country \* \* \* more than one year prior to the date of the application for patent in the United States."

The knowledge thus made available to the public must, if it is to anticipate an invention, be practical and complete. As stated in Sec. 227 of Robinson on Patents:

"It is to be remembered, however, that 'knowledge,' in this sense, means such an acquaintance with the invention, on the part of the public, as renders it available to them as a practically operative means. If their knowledge is derived from use in this country, the use must be of such a kind as imparts this information. If it rests on any foreign or domestic patent or publication these must be sufficient to accomplish the same result. In neither of these cases must there be any necessity for the exercise of additional inventive skill, since with the employment of the creative faculties, in the adaptation of any invention to the public use, another obligation is incurred which can only be discharged by protecting that inventor in the exclusive use of the invention. Thus we arrive at a more perfect and exhaustive definition of this attribute of novelty, and see that an invention is to be regarded as new whenever it has not already been brought within the practical knowledge of the public as an operative means, either through prior use at home, or through a prior patent or a prior publication."

In view of the foregoing considerations, it would appear that if section 102 (b) was to be given a different interpretation as to plant patents, it should have been expressly qualified by Congress so that descriptions of plants in printed publications would have been judged by different standards than those so long recognized by leading text writers and the courts. Since no such qualification exists we must, under 35 U.S.C. § 161, apply to the descriptions in the instant publications the same requirements as have been applied to the descriptions in publications in cases dealing with patents on other inventions.

Basically, section 102(b) requires that an inventor, who has placed his invention in the public domain, file his application within one year thereafter or within a year of the time when anyone else may have made it available to the public. Section 102(b) is a recognition that early publication of inventions is to be encouraged and thus does not bar the granting of a patent if the application therefor be filed within one year from the date of the printed publication.

The public purpose of section 102(b) is clear enough, and has been enunciated or assumed in the very considerable body of decisional law in which the clause "described in a printed publication" has been interpreted with respect to whether the publication has in fact conveyed such knowledge of an invention to the public as to put the public in possession of the invention.

[2] The briefs of the parties in the instant case support their opposed conclusions by reference to the ample case law, which sets forth particular standards as to what constitutes a "publication." We think the controlling view here is that stated in *Seymour v. Osborne*, 11 Wall. 516, at page 555, 78 U.S. 516, at page 555, 20 L.Ed. 33 (1870), where the court said:

"Patented inventions cannot be superseded by the mere introduction of a foreign publication of the kind, though of prior date, unless the description and drawings contain and exhibit a substantial representation of the patented improvement, in such full, clear, and exact terms as to enable any person skilled in the art or science to which it appertains, to make, construct, and practice the invention to the same practical extent as they would be enabled to do if the information was derived from a prior patent. Mere vague and general representations will not support such a defence, as the knowledge supposed to be derived from the publication must be sufficient to enable those skilled in the art or science to understand the nature and operation

of the invention, and to carry it into practical use. Whatever may be the particular circumstances under which the publication takes place, the account published, to be of any effect to support such a defence, must be an account of a complete and operative invention capable of being put into practical operation."

See also, *Wisconsin Alumni Research Foundation v. George A. Breon and Company, Inc.*, C.C.A. 8, 85 F.2d 166, cert. denied 299 U.S. 598, 57 S.Ct. 191, 81 L.Ed. 441 (1936), *Downton v. Yeager Milling Co.*, 108 U.S. 466, 3 S.Ct. 10, 27 L.Ed. 789; *Eames v. Andrews*, 122 U.S. 40, 66, 7 S.Ct. 1073, 30 L.Ed. 1064.

[3] We think it is sound law, consistent with the public policy underlying our patent law, that before any publication can amount to a statutory bar to the grant of a patent, its disclosure must be such that a skilled artisan could take its teachings in *combination with his own knowledge of the particular art and be in possession of the invention*. Such a doctrine is in accord with that expressed by the Supreme Court when it held patent No. 137,893 invalid in *Cohn v. United States Corset Co.*, 93 U.S. 366, 23 L.Ed. 907. The court stated (p. 377):

"\* \* \* the evidence shows that the Johnson specification, *in connection with the known state of the art at the time when it was filed and published*, was sufficient to enable one skilled in the art of corset-making and in the use of the jacquard to make the patented corset." [Emphasis ours.]

It is the position of appellant that the publications relied upon by the examiner and the Board of Appeals in rejecting his applications, are not "enabling" publications, i. e., the published information therein is not sufficient to enable anyone of ordinary skill in the art of plant breeding to practice the invention and produce the disclosed varieties of *rosa floribunda* plants. The validity of appellant's position can be appraised only after one understands the general techniques by

which a rose breeder produces a new rose variety.

Commercial rose-breeders, particularly in this country and England, continually strive to develop new varieties with characteristics of interest to commercial and amateur rose growers. A few of these characteristics are color, fragrance, freedom from various diseases, abundant foliage, firmness, size and shape of flower, number and frequency of blooms, etc. Each of these characteristics is a sex-linked characteristic and as such is subject to the applicable principles of plant heredity and the transmission of inheritable characteristics. The Encyclopedia Britannica (1957), states that the number of hybridized roses introduced commercially each year is over one hundred. Roses have been cultivated for so many centuries and have been hybridized so extensively that it is difficult to refer the cultivated forms to wild prototypes. To facilitate grouping varieties with similar characteristics, a horticultural classification has evolved which is complicated and often inconsistent, since there is considerable overlapping and emergence of classes as the result of intensive interbreeding. A comprehensive list given in J. H. McFarland's Modern Roses IV, 1952, includes some 6,150 names which represents only a small proportion of the roses hybridized and named during the preceding 250 years. Due to the number of variable characteristics, no two varieties, even if from identical parentage, are exactly alike. It has aptly been said by Florence Coates in "The Poetry of Earth" that:

"There is always room for beauty:  
memory

A myriad lovely blossoms may en-  
close

But, whatsoe'er hath been there  
still must be

Room for another rose".

After determining the characteristics desired in a new rose, the rose breeder

selects the parent plants for certain of their known characteristics. By the process of cross-pollination a seed is formed in one of the parent plants as the result of the union of each pair of sex cells contributed by the parent plants. Propagation from the resulting seeds is "sexual propagation", which is to be distinguished from "asexual propagation", in that in "sexual propagation" the parent plants each contribute to the formation of the embryo that will develop in the seed and eventually give rise to a plant which differs from either of the parent plants as well as from other plants produced from other seeds resulting from the same cross-pollination. In "asexual propagation," however, the plant is propagated by divisions or cuttings to form clones, each of which is identical to the parent plant and to all other cuttings or clones taken from the parent.<sup>4</sup>

The rose breeder strives to produce by *sexual* propagation a rose having the desired characteristics, after which this particular rose with the desirable characteristics is further propagated by *asexual* methods in which all of the characteristics of that one rose plant, and only that plant, are transmitted to the new plants derived by cutting, etc.

The *rosa floribunda* plants described in the two applications on appeal and in the publications were produced by sexual propagation as the result of the chance arrangement of the almost infinite number of variables arising from the particular chromosomes of the parent plants. The parentage of the "Dusky Maiden" rose is not disclosed in the publications. The parentage of the "Charming Maid" rose is given in the Rose Annual of 1954 as "Dainty Maiden x Mrs. Sam McGredy." To those skilled in the art of rose breeding this indicates that the parent "Dainty Maiden" is the seed parent, i. e., that this parent was selected by the breeder to bear and develop the seeds which result from pollination of its emasculated flowers with pollen taken

4. "Fundamentals in Plant Breeding" by Samuel L. Emsweller, Plants and Gardens, Summer, 1959.

from the other parent, "Mrs. Sam McGredy."<sup>5</sup>

The production of seeds by cross-pollination does not assure the plant breeder that he has produced a true new plant variety having the characteristics desired. At this step, the principles of heredity and plant genetics introduce such variables that no two seeds from the parent cross can be expected to produce identical plants.

The functions of the chromosomes and genes in transmitting inheritable properties from parents to offspring in plant breeding are brought into play only when the nuclei from different parent plants fuse together to form, in the seed, the nucleus of the new plant. Differences in composition of the fusing nuclei produce an organism which differs from either parent. These differences may be due, for example, to the presence of a duplicated chromatin granule (gene) in one, which may be represented singly or not at all in the other.<sup>6</sup>

While man can and does assist nature by the cross-pollination of selected parent plants, the actual creation of the new plant, because of the almost infinite number of possible combinations between the genes and chromosomes, is not presently subject to a controlled reproduction by act of man. While those skilled in this art now understand the mechanics of plant reproduction and the general principles of plant heredity, they are not presently able to control the factors which govern the combinations of genes and chromosomes required to produce a new plant having certain predetermined desired properties. The plant breeder must time and again recall the lines of Tenny-

son's "Flower in the Crannied Wall." after he has completed cross-pollination of the parent stock and awaits the new offspring:

"Flower in the crannied wall,  
I pluck you out of the crannies,  
I hold you here, root and all, in my  
hand,  
Little flower—but if I could understand  
What you are, root and all, and all  
in all,  
I should know what God and Man  
is."

It is not until the rose breeder has germinated the sexually produced rose seeds from the selected parents and raised plants therefrom to blooming size that he can make the final selections of the individual plant or plants which are to be multiplied by asexual reproduction.

The *rosa floribunda* plants here in issue thus appear to be something more than Gertrude Stein may have observed when she wrote in "Sacred Emily" that "a rose is a rose is a rose is a rose".

In holding that the publications here in issue constitute a legal bar to a granting of patents on the *rosa floribunda* plants described in the applications here on appeal, we think the examiner and the Board of Appeals disregarded what we have found to be the legally imposed limitations on the meaning of the clause "described in a printed publication" in section 102(b) in the prior cases in which the courts have interpreted the clause in determining whether a particular description in a publication will constitute a statutory bar to the grant of a patent. We think the board and the examiner

5. Emasculation of the flower is accomplished by first cutting the petals at the base of a rose bud, then cutting the tip of the bud. The remainder of the pollination step is described in "Roses for the Home," U. S. Department of Agriculture, Home and Garden Bulletin No. 25 (issued May 1953, slightly revised March 1953), by S. L. Emsweller, W. D. McClellan, and Floyd F. Smith, at page 23, as follows:

"The emasculated flower is then covered with a paper bag to keep unwanted pollen

from reaching the stigma. In a day or two the stigma is covered with a sticky substance called stigmatic fluid. It is now receptive. Remove the bag, and place the pollen collected from the desired parent plant on the stigma with a camel's hair brush. The paper bag is replaced, and, if the cross-pollination is successful, a seed pod soon starts to form."

6. See Genetics and Eugenics—W. E. Castle, Harvard University Press, 1932 (4th Edition).



were incorrect in overlooking these cases and interpreting the clause "described in a printed publication" in section 102(b) according to what the examiner called "its exact and unequivocal meaning." When used in the Patent Act of 1952, this clause had acquired in the context in which it is used in section 102(b) something other than an "exact and unequivocal meaning" as a result of the judicially imposed limitation that this clause requires that the description of the invention in the printed publication must be an "enabling" description. Our study of the prior cases which have imposed this interpretation on the clause indicates that the proper test of a description in a publication as a bar to a patent as the clause is used in section 102(b) requires a determination of whether one skilled in the art to which the invention pertains could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention on which a patent is sought. Unless this condition prevails, the description in the printed publication is inadequate as a statutory bar to patentability under section 102(b).

[4] We do not agree with the examiner and the board that this creates an "anomaly" when dealing with plant patents which requires that "plant publications must be totally ignored as printed publications." In view of the long line of cases dealing with other types of inventions antedating 1930, we think Congress, by failing to provide otherwise, intended that the provisions of section 102 (b), as applied to plant patents, should not be interpreted otherwise than they had been with respect to other inventions, i. e., that only an "enabling" publication is effective as a bar to a subsequent

patent. We do not agree with the view expressed by the examiner that this necessarily requires that plant publications be "totally ignored." Instead, it requires that the facts of each case be carefully considered to determine whether the description in the printed publication in question *does in fact* place the invention in the possession of the public. Each case must be decided on its own particular facts in determining whether, in fact, the description in the printed publication is adequate to put the public in possession of the invention and thus bar patentability of a plant under the conditions stated in section 102(b). While the present knowledge of plant genetics may mean as a practical matter, that the descriptions in such general publications as are here involved cannot be relied upon as a statutory bar under section 102(b), we must be mindful of the scientific efforts which are daily adding to the store of knowledge in the fields of plant heredity and plant eugenics<sup>7</sup> which one skilled in this art will be presumed to possess.

The patent law, as shown by the Committee Reports, was extended to plant patents in order to stimulate interest in the breeding and commercial development of new and valuable plant species. To erect technical barriers to the grant of such patents by a strict and literal interpretation of the clause "described in a printed publication" in section 102(b) as was done by the examiner and Board of Appeals, apparently without consideration of the public purpose underlying the plant patent provisions, seems to us will defeat the purpose of the act by creating conditions for barring plant patents which are different from the long recognized conditions for barring patents on other inventions.

The decision of the board cites numerous decisions as support for its affirmance

7. While many such studies undoubtedly are in progress, some idea of the possible additions to the knowledge of plant heredity is found in current seed catalog offerings of peanut seeds which by atomic irradiation will produce plants in which the peanuts are produced above the ground. The chemical colchicine also is

widely used to modify genetic characteristics of seeds. Current studies to "break the chromosome code" may also add to the knowledge of plant breeders so that they may someday secure possession of a plant invention by a description in a printed publication as is now possible in other fields of inventive effort.



of the examiner's rejection. It is our view that these decisions either have not been properly interpreted by the board in relying on them to support its view or that they are not controlling upon the issue here.

The board relies heavily on *Cohn v. United States Corset Co.*, supra, which in the solicitor's brief has been characterized as "the landmark case on this aspect of the law," and is relied upon as support for the assertion that "the overwhelming weight of authority supports the proposition that a clear naked description in a prior publication is sufficient under the law to bar a subsequent inventor from obtaining a patent on the identical thing."<sup>8</sup> That the Cohn case did not so hold seems clear to us. However, in view of the reliance placed upon language used in that case and upon the number of cases which agree with the position of the solicitor concerning what the Cohn case is alleged to hold, we shall here discuss the Cohn case in some detail.

The Cohn case involved a suit for infringement of the Cohn patent on a corset which contained the following claim:

"A corset having the pockets for the reception of the bones formed in the weaving, and varying in length relatively to each other, as desired, substantially in the manner and for the purpose set forth."

The defense of invalidity of the Cohn patent was predicated, under a statute which corresponds to 35 U.S.C. § 102(a), on an English provisional specification of one John Henry Johnson as a *prior publication* which was asserted to *disclose* the Cohn invention. The pertinent part of the Johnson disclosure stated:

"This invention related to the manufacture of what are known as woven corsets, and consists in the employment of the jacquards in the loom,

one of which effects the shape or contour of the corset, and the other the formation of the double portions of slots for the introduction of the whalebones. These slots or double portions are made simultaneously with the single parts of the corset; and, in place of being terminated in a point, they are finished square off, and at *any required length* in the corset, instead of always running the entire length, as is usually the case in woven corsets." [Emphasis ours.]

Referring to the Johnson disclosure, the court stated (p. 370):

"It is, therefore, fatal to the validity of the plaintiff's patent if, in fact, it does *describe sufficiently* the manufacture described and claimed in his specification. It must be admitted that, unless the earlier printed and published description does exhibit the later patented invention in such a full and intelligible manner as to *enable persons skilled in the art to which the invention is related to comprehend it without assistance from the patent*, or to make it, or repeat the process claimed, it is insufficient to invalidate the patent." [Emphasis ours.]

The court further stated (p. 373):

"But the claim must be further limited in view of the state of the art when the application for the patent was made. \* \* \* For more than twenty years it has been customary to weave in these gussets bone-pockets stopped off or closed in the weaving at various distances from the edge of the corset.

\* \* \* \* \*

"It is manifest, then, that there is nothing in the plaintiff's patent which was not described in the Johnson specification, unless it be that the closed slots or cases mentioned

8. In considering this assertion, it should be borne in mind that we are here dealing with an alleged description in a printed publication of applicant's own roses, whereas in the Cohn case, the description in the printed publication was that of an

invention made by a prior inventor, thus in a strict sense, the Cohn case is dealing with a situation covered by 35 U.S.C. § 102(a) rather than the technical bar of 35 U.S.C. § 102(b).

in the former are required to be woven of varying length. A variation in the length of the pockets relatively to each other, as desired, is, as we have seen, the sole distinctive feature of the plaintiff's invention. *But it was well known before Johnson filed his specification that the bone-pockets of a corset must vary in length.* (93 U.S. at 375) [Emphasis ours.]

\* \* \* \* \*

"Every person skilled in corset making knew the necessity of such variation. \* \* \*" (93 U.S. at 376)

The crux of the Cohn decision as we see it is:

"\* \* \* the evidence shows that the Johnson specification, in connection with the known state of the art at the time when it was filed and published, was sufficient to enable one skilled in the art of corset-making and in the use of the jacquard to make the patented corset." (93 U.S. at 377.) [Emphasis ours.]

It is in the light of these comments by the court that the true significance of its statements, which the Patent Office and numerous cases quote as to the holding in the Cohn case, can be determined. The court said (p. 377):

"It is quite immaterial, even if it be a fact, that the Johnson specification is sufficient to teach a manufacturer *how to make* the patented corset. It is enough if it sufficiently describes the corset itself. Neither it nor the plaintiff's specification exhibits the process of making. Neither of them set up a claim for a process. The plaintiff claims a manufacture, not a mode of making it; and the important inquiry, therefore, is, whether the prior publication *described* the article. To defeat a party suing for an infringement, it is sufficient to plead and prove that the thing patented to him had been patented or *described in some printed publication* prior to his sup-

posed invention or discovery thereof. \* \* \* It is enough for this case that the invention patented to the plaintiff was *clearly described* in 1854, in the printed publication of the Johnson (Geresme) provisional specification." [Emphasis added.]

The court throughout its opinion in the Cohn case *directly* referred to those skilled in the art, and the knowledge which they possessed. We think it is because of this knowledge, and only because of this knowledge, that the court said "the important inquiry, therefore, is, whether the prior publication described the article."

The solicitor also cites in support of the board's position, the decision of the District Court of Maryland in *One-Piece Bifocal Lens Co. v. Bisight Co.*, 246 F. 450, mod. 259 F. 275 (CCA 4), cert. den. 249 U.S. 606, 39 S.Ct. 288, 63 L.Ed. 799. At page 457, of 246 F. the Court stated:

"The description under consideration is one which does not tell how to make the article it describes. It is one published at a time when those skilled in the art would not either from its disclosures or their knowledge, or from both combined, know how to produce it. For the reasons already stated, it is believed that, even under such circumstances, it may anticipate a later patent."

Prior to this statement the District Court discussed the Cohn case and, basing its analysis of that decision upon the language on page 377 last quoted *supra*, stated on page 456:

"Is the force of this language materially weakened by the fact that the court went on to point out that what was known at the time the anticipating Johnson's specification was filed, was sufficient to enable one skilled in the art to make the corset?"

In view of our analysis of the Cohn case, *supra*, we answer the District Court's question in the affirmative. The standard for publications applied by the

District Court is somewhat uncertain, since it is stated that the publication "*may anticipate a later patent.*" [Emphasis added.] Whatever may have been its position, we do not agree, as stated supra, with its analysis of the Cohn case.

The case of General Electric Co. v. De Forest Radio Co., 17 F.2d 90 (D.C.Del.), mod. 28 F.2d 641 (CCA 3), cert. den. 278 U.S. 656, 49 S.Ct. 180, 73 L.Ed. 565, is also cited in the solicitor's brief. In the General Electric case, the court stated in essence that a publication which evidences conception of an idea would be enough to "destroy the product claims in suit upon the ground that they are wanting in invention." As its authority, the court cited the Bifocal case, which, as we have previously discussed, based its decision on what we think is an erroneous interpretation of the Cohn case. We therefore decline to accept the statement in the General Electric case as controlling.

The Patent Office also relies upon several additional decisions of this court which are alleged to support its position. Among these cases are: In re Marden and Rentschler, 48 F.2d 428, 18 CCPA 1119; In re Attwood, 253 F.2d 234, 45 CCPA 824; In re Von Bramer et al., 127 F.2d 149, 29 CCPA 1018; In re Crosley et al., 159 F.2d 735, 34 CCPA 882; In re Fink, 62 F.2d 103, 20 CCPA 716; In re Stoll et al., 161 F.2d 241, 34 CCPA 1058; In re Michalek, 162 F.2d 229, 34 CCPA 1124; In re Shackell, 194 F.2d 720, 39 CCPA 847; In re Kebrich, 201 F.2d 951, 40 CCPA 780; In re Inman, 228 F.2d 229, 43 CCPA 709; In re Baranaukas et al., 228 F.2d 413, 43 CCPA 727.

In none of these decisions do we find any support for the position taken by the Patent Office nor anything inconsistent with our position in the instant case.

The Attwood case concerned use, as a reference, of a prior patent which was said by the appellant to cover an inoperative disclosure. The court based its decision on the Marden and Rentschler and Von Bramer cases. The Marden and Rentschler case cited the Cohn case and,

erroneously interpreting that decision, merely stated on page 429 of 48 F.2d, on page 1121 of 18 CCPA that:

"Ductile thorium and the products produced therefrom and claimed in appellants' application were clearly and adequately described in the references of record. Accordingly, in view of the decisions hereinbefore referred to, the question of the operativeness of the methods disclosed in the references is not involved in a determination of the issue of the patentability of the subject-matter of the involved claims."

The Von Bramer case also concerned a rejection based on a reference patent alleged to disclose an inoperative invention. The court held that "It is not necessary that a reference patent for a device or chemical compound disclose an operative process for reproducing the article or product." Authority cited for this proposition was the Cohn, Marden, Bifocal and other cases.

Implicit in all of these cases is the concept of a certain degree of knowledge possessed by one skilled in the arts involved concerning the disclosure of the prior publication and the concept which was sought to be patented, to the end *that this knowledge taken with the disclosure of the printed publications*, was sufficient to place the disclosed invention in the possession of the public. To the extent, if any, that these decisions may conflict with this analysis of the Cohn case, we disagree with them and do not find them conclusive of the issue here.

In the Michalek case, the court stated that skilled workers would, as a matter of course, be able to utilize the process disclosed by the reference to get results within the limits of the product claims of the application at bar. We think this fact situation is sufficient to distinguish this case.

The Board of Appeals cited Merck and Co., Inc. v. Marzall, 91 U.S.App.D.C. 50, 197 F.2d 206. Contrary to the Board of Appeals' position, this case is believed to substantiate the conclusions we have

here reached. The court stated in the Merck case:

"We are dealing solely with an application for a patent on the *compound* itself. Such an application must be denied if there has been any prior disclosure of the compound, even though no practical means for its isolation or manufacture was previously known." [Emphasis ours.]

In 197 F.2d at page 208, the court in footnote 2 sets forth the knowledge which existed at the time the invention was made. It is therein stated:

"2. A witness called by plaintiffs-appellants testified on cross-examination:

\* \* \* \* \*

"Q. Now, with thiamin monobromide at hand, would there have been any difficulty for you as an organic chemist to prepare the thiamin mononitrate?

"A. I think if I had been asked at the time that this application was filed to prepare thiamin mononitrate I would have come up with it in very short order. I was confident that such a compound was capable of existence and could be made.

"Q. With little difficulty? A. Yes."

We think the Merck case must be read in the light of the fact that the knowledge of chemists skilled in producing the compound there in issue was such that a mere disclosure of the chemical constitution of the compound was enough to allow such chemists to produce the disclosed compound. Even in the chemical art, however, where the knowledge of skilled artisans is great, there are limitations on the availability of disclosures in printed publications as bars under section 102 (b).

In the Baranaukas case, this court said, after considering several of the above cases, "we feel constrained to point out that there are limits to the doctrine of those cases \* \* \*. Certainly they do not extend so far as to permit publication of theoretical lists of hundreds or

thousands of possible compounds to deny patent protection on such compounds to those who actually discovered them later."

In *Shell Development Co. v. Watson*, D.C., 149 F.Supp. 279, affirmed 102 U.S. App.D.C. 297, 252 F.2d 861, which the Patent Office further cites to support its position, the court relied on the Merck case and stated further:

"A clear description in a prior publication is all that is necessary under the law to bar a subsequent inventor from obtaining a patent on the identical thing. In other words, a prior publication, in order to defeat a patent, need only exhibit the thing claimed in such an intelligible manner as to *enable persons skilled in the art to which the invention is related, to comprehend* it. Defendant's refusal to grant the claim sought here based upon the Ring Index publication was proper for the Court holds that the name and the structural formula contained in the Ring Index publication constitutes a sufficient description to anticipate. Plaintiff's claim 13 is clearly described in the publication within the meaning of the statutory language. I find for the defendant." [Emphasis ours.]

The court in the Shell case cited the Merck case as its authority. It is therefore in this light that we must construe the court's use of the word *comprehend*. So construed, the Shell case holds that the publication *in the light of the knowledge possessed by those skilled in the art* was sufficient to bar the grant of a patent. We do not find this to be inconsistent with our holding based on contrary facts in the case at bar.

Finally, there is the decision of *In re Decker*, 1911 C.D. 274, 36 App.D.C. 104, 162 O.G. 999. In this case, as in others which we have previously discussed, the holding of the Cohn case is believed to have been erroneously construed because of an incomplete analysis of the entire opinion of the court. In the Decker case the court said "the [Cohn] court held a

patent for a corset invalid on the ground that it had been fully described in a prior English patent, although the prior patent contained no description of the device by which the corset could be made." To this we again add the all-important words of the court in the Cohn case, that "the known state of the art at the time when \* \* \* [the Johnson specification] \* \* \* was filed and published, was sufficient to enable one skilled in the art of corset-making and in the use of the jacquard to make the patented corset." [Emphasis ours.]

### CONCLUSION

[5] We therefore hold that descriptions in printed publications of new plant varieties, before they may be used as statutory bars under 35 U.S.C. § 102(b), must meet the same standards which must be met before a description in a printed publication becomes a bar in non-plant patent cases. 35 U.S.C. § 161 does not contain any limitation on this interpretation of the clause "described in a printed publication," and Congress has not "otherwise provided." When so considered, the descriptions in the printed publications here in issue do not meet the requirement of an "enabling" description, as the statute has been interpreted in numerous cases.

The Board of Appeals stated in its decision below that "it is no more absurd to use a disclosure which is not enabling as a bar than it is to grant a patent on such a disclosure; the disclosure in the specifications of these applications are admittedly just as unenabling as the disclosures of the publications." The answer to this apparent anomaly lies in 35 U.S.C. § 162 in which Congress "otherwise provided" by specifically allowing for such a description in plant patent applications.

*No such allowance has been made in 35 U.S.C. § 102(b) with reference to the sufficiency of the description of new plant varieties in printed publications.*

Another answer to this apparent "anomaly" is implicit in 35 U.S.C. § 163. The plant patent grant differs from that given with respect to other inventions. Infringers must be shown to have asexually reproduced or sold or used the plant on which the patent was granted. Cf. *Cole v. Youdath*, supra, *Kim Bros. v. Hagler*, supra, and *Armstrong Nurseries, Inc. v. Smith et al.*, supra. This section implicitly recognizes there is no possibility of producing the plant from a disclosure as 35 U.S.C. § 112 contemplates. Therefore, there is no requirement for any how-to-make disclosure in the application for a plant patent.

The mere description of the plant is not necessarily an "enabling" disclosure. Such descriptions, just as in the case of other types of inventions, in order to bar the issuance of a patent, must be capable, when taken in conjunction with the knowledge of those skilled in the art to which they pertain, of placing the invention in the possession of those so skilled.

The descriptions of the new roses in the instant publications,<sup>9</sup> are incapable of placing these roses in the public domain by their descriptions when interpreted in the light of the knowledge now possessed by plant breeders. The roses disclosed in the appealed applications are not, therefore, "described in a printed publication" within the meaning of 35 U.S.C. § 102(b).

The decision of the Board of Appeals is reversed.

Reversed.

MARTIN, J., sat but did not participate because of illness.

9. An analogy also may be drawn between the pictures of the roses shown in the printed publications and pictures of machines in printed publications which have been held to be insufficient descriptions of the patented invention. See footnote 1, *Robinson on Patents*, Sec. 326, in which it is stated:

"That a picture or drawing without printed text is not a publication, see *New Process Fermentation Co. v. Koch* (C.C.1884), 21 F. 590; 20 O.G. 535; *Reeves v. Keystone Bridge Co.* (1872), Fed.Cas.No.11,600, 1 O.G. 406, 5 Fish. Pat.Cas. 456, 9 Phila. 365; *Judson v. Cope* (1860), Fed.Cas.No.7,565, 1 Bond 327, 1 Fish.Pat.Cas. 615."

ant as well as the public interest, the Commission abuses its discretion by declining to release the bond merely because of sales by a respondent of goods known to the complainant at the time of the agreement.

Biocraft also makes other arguments which we need not address.

### CONCLUSION

The Commission's denials of Biocraft's requests for return or cancellation of bonds posted pursuant to the Temporary Cease and Desist Order issued January 10, 1990, were an abuse of discretion. Its order is therefore

REVERSED.



In re Mark A. VAECK, Wipa  
Chungjatupornchai and  
Lee McIntosh.

No. 91-1120.

United States Court of Appeals,  
Federal Circuit.

Oct. 21, 1991.

Inventor sought patent for claimed invention directed to use of genetic engineering techniques for production of insecticidal proteins. The United States Patent and Trademark Office Board of Patent Appeals and Interferences affirmed an examiner's rejection of certain claims, and appeal was taken. The Court of Appeals, Rich, Circuit Judge, held that: (1) patent application was improperly rejected on ground of prima facie obviousness, and (2) patent application was properly rejected to extent that claims were too general to enable person skilled in art to make and use claimed invention without undue experimentation.

Affirmed in part, reversed in part.

Mayer, Circuit Judge, dissented and filed opinion.

#### 1. Patents ⇨314(5)

Obviousness of invention for which patent is sought is legal question which court independently reviews, though based upon Patent and Trademark Office's underlying factual findings, which court reviews under clearly erroneous standard. 35 U.S.C.A. § 103.

#### 2. Patents ⇨16(2)

In reviewing rejection of invention for patent as obvious in view of combination of prior art references, court considers whether prior art would have suggested to those of ordinary skill in art that they should make claimed composition or device, or carry out claimed process, and whether prior art would also have revealed that in so making or carrying out, those of ordinary skill would have reasonable expectation of success; both suggestion and reasonable expectation of success must be found in prior art, not in applicant's disclosure. 35 U.S.C.A. § 103.

#### 3. Patents ⇨16.25

Patent application for genetic engineering techniques for production of insecticidal proteins was improperly rejected on ground of prima facie obviousness; prior art did not disclose or suggest expression in cyanobacteria of chimeric gene encoding insecticidally active protein, or convey to those of ordinary skill reasonable expectation of success in doing so. 35 U.S.C.A. § 103.

#### 4. Patents ⇨99

To be patentable, specification of patent must enable any person skilled in art to which it pertains to make and use claimed invention without undue experimentation. 35 U.S.C.A. § 112.

#### 5. Patents ⇨99

Patent application for using genetic engineering techniques to produce insecticidal proteins was properly rejected to extent that claims were too general to enable person skilled in art to make and use claimed invention without undue experimentation;

claim referred to use of cyanobacteria in general as host organism, despite fact that cyanobacteria were diverse and relatively poorly studied group of organisms, comprising some 150 different genera, with successful use of any one type in manner called for in invention being unpredictable. 35 U.S.C.A. § 112.

#### 6. Patents ⇐99

Although patent applicants are not required to disclose every species encompassed by their claims, even in unpredictable art, in order to satisfy enablement requirement for patentability, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use invention as broadly as it is claimed. 35 U.S.C.A. § 112.

Ian C. McLeod, Ian C. McLeod, P.C., Okemos, Mich., argued for appellant.

Teddy S. Gron, Associate Sol., Office of the Sol., of Arlington, Va., argued for appellee. With him on the brief were Fred E. McKelvey, Sol. and Richard E. Schafer, Associate Sol.

Before RICH, ARCHER, and MAYER, Circuit Judges.

RICH, Circuit Judge.

This appeal is from the September 12, 1990 decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), affirming the examiner's rejection of claims 1-48 and 50-52 of application Serial No. 07/021,405, filed March 4, 1987, titled "Hybrid Genes Incorporating a DNA Fragment Containing a Gene Coding for an Insecticidal Protein, Plasmids, Transformed Cyanobacteria Expressing Such Protein and Method for Use as a Biocontrol Agent" as unpatentable under 35 U.S.C. § 103, as well as the rejection

of claims 1-48 and 50-51 under 35 U.S.C. § 112, first paragraph, for lack of enablement. We reverse the § 103 rejection. The § 112 rejection is affirmed in part and reversed in part.

## BACKGROUND

### A. The Invention

The claimed invention is directed to the use of genetic engineering techniques<sup>1</sup> for production of proteins that are toxic to insects such as larvae of mosquitos and black flies. These swamp-dwelling pests are the source of numerous human health problems, including malaria. It is known that certain species of the naturally-occurring *Bacillus* genus of bacteria produce proteins ("endotoxins") that are toxic to these insects. Prior art methods of combatting the insects involved spreading or spraying crystalline spores of the insecticidal *Bacillus* proteins over swamps. The spores were environmentally unstable, however, and would often sink to the bottom of a swamp before being consumed, thus rendering this method prohibitively expensive. Hence the need for a lower-cost method of producing the insecticidal *Bacillus* proteins in high volume, with application in a more stable vehicle.

As described by appellants, the claimed subject matter meets this need by providing for the production of the insecticidal *Bacillus* proteins within host cyanobacteria. Although both cyanobacteria and bacteria are members of the procaryote<sup>2</sup> kingdom, the cyanobacteria (which in the past have been referred to as "blue-green algae") are unique among procaryotes in that the cyanobacteria are capable of oxygenic photosynthesis. The cyanobacteria grow on top of swamps where they are consumed by mosquitos and black flies. Thus, when *Bacillus* proteins are produced with-

1. Basic vocabulary and techniques for gene cloning and expression have been described in *In re O'Farrell*, 853 F.2d 894, 895-99, 7 U.S.P.Q.2d 1673, 1674-77 (Fed.Cir.1988), and are not repeated here.

2. All living cells can be classified into one of two broad groups, procaryotes and eucaryot s.

The procaryotes comprise organisms formed of cells that do not have a distinct nucleus; their DNA floats throughout the cellular cytoplasm. In contrast, the cells of eucaryotic organisms such as man, other animals, plants, protozoa, algae and yeast have a distinct nucleus wherein their DNA resides.



in transformed<sup>3</sup> cyanobacterial hosts according to the claimed invention, the presence of the insecticide in the food of the targeted insects advantageously guarantees direct uptake by the insects.

More particularly, the subject matter of the application on appeal includes a chimeric (i.e., hybrid) gene comprising (1) a gene derived from a bacterium of the *Bacillus* genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing<sup>4</sup> the *Bacillus* gene in a host cyanobacterium, so as to produce the desired insecticidal protein.

The claims on appeal are 1-48 and 50-52, all claims remaining in the application. Claim 1 reads:

1. A chimeric gene capable of being expressed in Cyanobacteria cells comprising:

(a) a DNA fragment comprising a promoter region which is effective for expression of a DNA fragment in a Cyanobacterium; and

(b) at least one DNA fragment coding for an insecticidally active protein produced by a *Bacillus* strain, or coding for an insecticidally active truncated form of the above protein or coding for a protein having substantial sequence homology to the active protein,

the DNA fragments being linked so that the gene is expressed.

Claims 2-15, which depend from claim 1, recite preferred *Bacillus* species, promoters, and selectable markers.<sup>5</sup> Independent claim 16 and claims 17-31 which depend therefrom are directed to a hybrid plasmid vector which includes the chimeric gene of claim 1. Claim 32 recites a bacterial strain. Independent claim 33 and claims 34-48 which depend therefrom recite a cyanobac-

terium which expresses the chimeric gene of claim 1. Claims 50-51 recite an insecticidal composition. Claim 52 recites a particular plasmid that appellants have deposited.

### B. Appellants' Disclosure

In addition to describing the claimed invention in generic terms, appellants' specification discloses two particular species of *Bacillus* (*B. thuringiensis*, *B. sphaericus*) as sources of insecticidal protein; and nine genera of cyanobacteria (*Synechocystis*, *Anacystis*, *Synechococcus*, *Agmenellum*, *Aphanocapsa*, *Gloecapsa*, *Nostoc*, *Anabaena* and *Ffremyllia*) as useful hosts.

The working examples relevant to the claims on appeal detail the transformation of a single strain of cyanobacteria, i.e., *Synechocystis* 6803. In one example, *Synechocystis* 6803 cells are transformed with a plasmid comprising (1) a gene encoding a particular insecticidal protein ("B.t. 8") from *Bacillus thuringiensis* var. *israelensis*, linked to (2) a particular promoter, the P<sub>L</sub> promoter from the bacteriophage Lambda (a virus of *E. coli*). In another example, a different promoter, i.e., the *Synechocystis* 6803 promoter for the rubisco operon, is utilized instead of the Lambda P<sub>L</sub> promoter.

### C. The Prior Art

A total of eleven prior art references were cited and applied, in various combinations, against the claims on appeal.

The focus of Dzelzkalns,<sup>6</sup> the primary reference cited against all of the rejected claims, is to determine whether chloroplast promoter sequences can function in cyanobacteria. To that end Dzelzkalns discloses the expression in cyanobacteria of a chimeric gene comprising a chloroplast promot-

DNA) via messenger RNA to ribosomes where a specific protein is made.

5. In the context of the claimed invention, "selectable markers" or "marker genes" refer to antibiotic-resistance conferring DNA fragments, attached to the gene being expressed, which facilitate the selection of successfully transformed cyanobacteria.

6. 12 *Nucleic Acids Res.* 8917 (1984).

3. "Transformed" cyanobacteria are those that have successfully taken up the foreign *Bacillus* DNA such that the DNA information has become a permanent part of the host cyanobacteria, to be replicated as new cyanobacteria are generated.

4. "Expression" of a gene refers to the production of the protein which the gene encodes; more specifically, it is the process of transferring information from a gene (which consists of



er sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT).<sup>7</sup> Importantly, Dzelzkalns teaches the use of the CAT gene as a "marker" gene; this use of antibiotic resistance-conferring genes for selection purposes is a common technique in genetic engineering.

Sekar I,<sup>8</sup> Sekar II,<sup>9</sup> and Ganesan<sup>10</sup> collectively disclose expression of genes encoding certain *Bacillus* insecticidal proteins in the bacterial hosts *B. megaterium*, *B. subtilis* and *E. coli*.

Friedberg<sup>11</sup> discloses the transformation of the cyanobacterium *Anacystis nidulans* R2 by a plasmid vector comprising the O<sub>L</sub>P<sub>L</sub> operator-promoter region and a temperature-sensitive repressor gene of the bacteriophage Lambda. While the cyanobacteria are attractive organisms for the cloning of genes involved in photosynthesis, Friedberg states, problems may still be encountered such as suboptimal expression of the cloned gene, detrimental effects on cell growth of overexpressed, highly hydrophobic proteins, and rapid turnover of some gene products. To address these problems, Friedberg teaches the use of the disclosed Lambda regulatory signals in plasmid vehicles which, it states, have "considerable potential for use as vectors the expression of which can be controlled in *Anacystis*...."

Miller<sup>12</sup> compares the initiation specificities *in vitro* of DNA-dependent RNA polymerases<sup>13</sup> purified from two different species of cyanobacteria (*Fremyella diplosiphon* and *Anacystis nidulans*), as well as from *E. coli*.

7. Chloramphenicol is an antibiotic; CAT is an enzyme which destroys chloramphenicol and thus imparts resistance thereto.

8. 137 *Biochem. and Biophys. Res. Comm.* 748 (1986).

9. 33 *Gene* 151 (1985).

10. 189 *Mol. Gen. Genet.* 181 (1983).

11. 203 *Mol. Gen. Genet.* 505 (1986).

12. 140 *J. Bacteriology* 246 (1979).

13. RNA polymerase, the enzyme responsible for making RNA from DNA, binds at specific nucleotide sequences (promoters) in front of genes

Nierzwicki-Bauer<sup>14</sup> identifies in the cyanobacterium *Anabaena* 7120 the start site for transcription of the gene encoding *rbcL*, the large subunit of the enzyme ribulose-1,5-bisphosphate carboxylase. It reports that the nucleotide sequence 14-8 base pairs preceding the transcription start site "resembles a good *Escherichia coli* promoter," but that the sequence 35 base pairs before the start site does not.

Chauvat<sup>15</sup> discloses host-vector systems for gene cloning in the cyanobacterium *Synechocystis* 6803, in which the antibiotic resistance-conferring *neo* gene is utilized as a selectable marker.

Reiss<sup>16</sup> studies expression in *E. coli* of various proteins formed by fusion of certain foreign DNA sequences with the *neo* gene.

Kolowsky<sup>17</sup> discloses chimeric plasmids designed for transformation of the cyanobacterium *Synechococcus* R2, comprising an antibiotic-resistant gene linked to chromosomal DNA from the *Synechococcus* cyanobacterium.

Barnes, United States Patent No. 4,695,455, is directed to the treatment with stabilizing chemical reagents of pesticides produced by expression of heterologous genes (such as those encoding *Bacillus* proteins) in host microbial cells such as *Pseudomonas* bacteria. The host cells are killed by this treatment, but the resulting pesticidal compositions exhibit prolonged toxic activity when exposed to the environment of target pests.

in DNA, and then moves through the gene making an RNA molecule that includes the information contained in the gene. Initiation specificity is the ability of the RNA polymerase to initiate this process specifically at a site(s) on the DNA template.

14. 81 *Proc. Natl. Acad. Sci. USA* 5961 (1984).

15. 204 *Mol. Gen. Genet.* 185 (1986).

16. 30 *Gene* 211 (1984).

17. 27 *Gene* 289 (1984).

### D. The Grounds of Rejection

#### 1. The § 103 Rejections

Claims 1-6, 16-21, 33-38, 47-48 and 52 (which include all independent claims in the application) were rejected as unpatentable under 35 U.S.C. § 103 based upon Dzelzkalns in view of Sekar I or Sekar II and Ganesan. The examiner stated that Dzelzkalns discloses a chimeric gene capable of being highly expressed in a cyanobacterium, said gene comprising a promoter region effective for expression in a cyanobacterium operably linked to a structural gene encoding CAT. The examiner acknowledged that the chimeric gene and transformed host of Dzelzkalns differ from the claimed invention in that the former's structural gene encodes CAT rather than insecticidally active protein. However, the examiner pointed out, Sekar I, Sekar II, and Ganesan teach genes encoding insecticidally active proteins produced by *Bacillus*, and the advantages of expressing such genes in heterologous<sup>18</sup> hosts to obtain larger quantities of the protein. The examiner contended that it would have been obvious to one of ordinary skill in the art to substitute the *Bacillus* genes taught by Sekar I, Sekar II, and Ganesan for the CAT gene in the vectors of Dzelzkalns in order to obtain high level expression of the *Bacillus* genes in the transformed cyanobacteria. The examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the expression of heterologous genes. In the absence of evidence to the

contrary, the examiner contended, the invention as a whole was *prima facie* obvious.

Additional rejections were entered against various groups of dependent claims which we need not address here. All additional rejections were made in view of Dzelzkalns in combination with Sekar I, Sekar II, and Ganesan, and further in view of other references discussed in Part C above.

The Board affirmed the § 103 rejections, basically adopting the examiner's Answer as its opinion while adding a few comments. The legal conclusion of obviousness does not require absolute certainty, the Board added, but only a reasonable expectation of success, citing *In re O'Farrell*, 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir.1988). In view of the disclosures of the prior art, the Board concluded, one of ordinary skill in the art would have been motivated by a reasonable expectation of success to make the substitution suggested by the examiner.

#### 2. The § 112 Rejection

The examiner also rejected claims 1-48 and 50-51 under 35 U.S.C. § 112, first paragraph, on the ground that the disclosure was enabling only for claims limited in accordance with the specification as filed. Citing *Manual of Patent Examining Procedure* (MPEP) provisions 706.03(n)<sup>19</sup> and (z)<sup>20</sup> as support, the examiner took the position that undue experimentation would be required of the art worker to practice the claimed invention, in view of the unpredictability in the art, the breadth of the claims, the limited number of working examples and the limited guidance provided

18. Denotes different species or organism.

19. MPEP 706.03(n), "Correspondence of Claim and Disclosure," provides in part:

In chemical cases, a claim may be so broad as to not be supported by [the] disclosure, in which case it is rejected as unwarranted by the disclosure....

20. MPEP 706.03(z), "Undue Breadth," provides in part:

[I]n applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Sol*, 1938 C.D. 723; 497 O.G.

546. This is because in arts such as chemistry it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield*, 1940 C.D. 351; 518 O.G. 255 gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." ...

in the specification. With respect to unpredictability, the examiner stated that

[t]he cyanobacteria comprise a large and diverse group of photosynthetic bacteria including large numbers of species in some 150 different genera including *Synechocystis*, *Anacystis*, *Synechococcus*, *Agmenellum*, *Nostoc*, *Anabaena*, etc. The molecular biology of these organisms has only recently become the subject of intensive investigation and this work is limited to a few genera. Therefore the level of unpredictability regarding heterologous gene expression in this large, diverse and relatively poorly studied group of procaryotes is high....

The Board affirmed, noting that: "the limited guidance in the specification, considered in light of the relatively high degree of unpredictability in this particular art, would not have enabled one having ordinary skill in the art to practice the broad scope of the claimed invention without undue experimentation. *In re Fisher*, 427 F.2d 833, 166 U.S.P.Q. 18 (CCPA 1970)."

## OPINION

### A. Obviousness

[1] We first address whether the PTO erred in rejecting the claims on appeal as prima facie obvious within the meaning of 35 U.S.C. § 103. Obviousness is a legal question which this court independently reviews, though based upon underlying factual findings which we review under the clearly erroneous standard. *In re Woodruff*, 919 F.2d 1575, 1577, 16 U.S.P.Q.2d 1934, 1935 (Fed.Cir.1990).

[2] Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have

a reasonable expectation of success. See *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir.1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

[3] We agree with appellants that the PTO has not established the prima facie obviousness of the claimed subject matter. The prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so. More particularly, there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding *Bacillus* insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes.

The PTO argues that the substitution of insecticidal *Bacillus* genes for CAT marker genes in cyanobacteria is suggested by the secondary references Sekar I, Sekar II, and Ganesan, which collectively disclose expression of genes encoding *Bacillus* insecticidal proteins in two species of host *Bacillus* bacteria (*B. megaterium* and *B. subtilis*) as well as in the bacterium *E. coli*. While these references disclose expression of *Bacillus* genes encoding insecticidal proteins in certain transformed bacterial hosts, nowhere do these references disclose or suggest expression of such genes in transformed cyanobacterial hosts.

To remedy this deficiency, the PTO emphasizes similarity between bacteria and cyanobacteria, namely, that these are both procaryotic organisms, and argues that this fact would suggest to those of ordinary skill the use of cyanobacteria as hosts for expression of the claimed chimeric genes. While it is true that bacteria and cyanobacteria are now both classified as procaryotes, that fact alone is not sufficient to motivate the art worker as the PTO con-

tends. As the PTO concedes, cyanobacteria and bacteria are not identical; they are classified as two separate divisions of the kingdom Procaryotae.<sup>21</sup> Moreover, it is only in recent years that the biology of cyanobacteria has been clarified, as evidenced by references in the prior art to "blue-green algae." Such evidence of recent uncertainty regarding the biology of cyanobacteria tends to rebut, rather than support, the PTO's position that one would consider the cyanobacteria effectively interchangeable with bacteria as hosts for expression of the claimed gene.

At oral argument the PTO referred to additional secondary references, not cited against any independent claim (i.e., Friedberg, Miller, and Nierzwicki-Bauer), which it contended disclose certain amino acid sequence homology between bacteria and cyanobacteria. The PTO argued that such homology is a further suggestion to one of ordinary skill to attempt the claimed invention. We disagree. As with the Dzelzkalns, Sekar I, Sekar II, and Ganesan references discussed above, none of these additional references disclose or suggest that cyanobacteria could serve as hosts for expression of genes encoding *Bacillus* insecticidal proteins. In fact, these additional references suggest as much about *differences* between cyanobacteria and bacteria as they do about similarities. For example, Nierzwicki-Bauer reports that a certain nucleotide sequence (i.e., the -10 consensus sequence) in a particular cyanobacterium resembles an *E. coli* promoter, but that another nearby nucleotide sequence (the -35 region) does not. While Miller speaks of certain promoters of the bacteriophage Lambda that are recognized by both cyanobacterial and *E. coli* RNA polymerases, it also discloses that these promoters exhibited differing strengths when exposed to the different polymerases. Differing sensitivities of the respective polymerases to an inhibitor are also disclosed, suggesting differences in the structures of the initiation complexes.

The PTO asks us to agree that the prior art would lead those of ordinary skill to conclude that cyanobacteria are attractive hosts for expression of any and all heterologous genes. Again, we can not. The relevant prior art does indicate that cyanobacteria are attractive hosts for expression of both native and heterologous *genes involved in photosynthesis* (not surprisingly, for the capability of undergoing oxygenic photosynthesis is what makes the cyanobacteria unique among procaryotes). However, these references do not suggest that cyanobacteria would be equally attractive hosts for expression of *unrelated* heterologous genes, such as the claimed genes encoding *Bacillus* insecticidal proteins.

In *O'Farrell*, this court affirmed an obviousness rejection of a claim to a method for producing a "predetermined protein in a stable form" in a transformed bacterial host. 853 F.2d at 895, 7 U.S.P.Q.2d at 1674. The cited references included a prior art publication (the Polisky reference) whose three authors included two of the three coinventor-appellants. The main difference between the prior art and the claim at issue was that in Polisky, the heterologous gene was a gene for ribosomal RNA, while the claimed invention substituted a gene coding for a predetermined protein. *Id.* at 901, 7 U.S.P.Q.2d at 1679. Although, as the appellants therein pointed out, the ribosomal RNA gene is not normally translated into protein, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein, and further predicted that if a gene coding for a protein were to be substituted, extensive translation might result. *Id.* We thus affirmed, explaining that

the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the [claimed] method could be used to make proteins.

....

21. *Stedman's Medical Dictionary* 1139 (24th ed. 1982) (definition of "Procaryota"). Procaryotic organisms are commonly classified according to the following taxonomic hierarchy: Kingdom;

Division; Class; Order; Family; Genus; Species. 3 *Bergey's Manual of Systematic Bacteriology* 1601 (1989).

... Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.

*Id.* at 901-02, 7 U.S.P.Q.2d at 1679-80.

In contrast with the situation in *O'Farrell*, the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art. Moreover, the "reasonable expectation of success" that was present in *O'Farrell* is not present here. Accordingly, we reverse the § 103 rejections.

### B. Enablement

[4] The first paragraph of 35 U.S.C. § 112 requires, *inter alia*, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without "undue experimentation." *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed.Cir.1988). That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *Id.* at 736-37, 8 U.S.P.Q.2d at 1404. Enablement, like obviousness, is a question of law which we independently review, although based upon underlying factual findings which we review for clear error. *See id.* at 735, 8 U.S.P.Q.2d at 1402.

[5] In response to the § 112 rejection, appellants assert that their invention is "pioneering," and that this should entitle them to claims of broad scope. Narrower claims would provide no real protection, appellants argue, because the level of skill in this art is so high, art workers could easily avoid the claims. Given the disclosure in their

specification, appellants contend that any skilled microbiologist could construct vectors and transform many different cyanobacteria, using a variety of promoters and *Bacillus* DNA, and could easily determine whether or not the active *Bacillus* protein was successfully expressed by the cyanobacteria.

The PTO made no finding on whether the claimed invention is indeed "pioneering," and we need not address the issue here. With the exception of claims 47 and 48, the claims rejected under § 112 are not limited to any particular genus or species of cyanobacteria. The PTO's position is that the cyanobacteria are a diverse and relatively poorly studied group of organisms, comprising some 150 different genera, and that heterologous gene expression in cyanobacteria is "unpredictable." Appellants have not effectively disputed these assertions. Moreover, we note that only one particular species of cyanobacteria is employed in the working examples of appellants' specification, and only nine genera of cyanobacteria are mentioned in the entire document.

Taking into account the relatively incomplete understanding of the biology of cyanobacteria as of appellants' filing date, as well as the limited disclosure by appellants of particular cyanobacterial genera operative in the claimed invention, we are not persuaded that the PTO erred in rejecting claims 1-46 and 50-51 under § 112, first paragraph. There is no reasonable correlation between the narrow disclosure in appellants' specification and the broad scope of protection sought in the claims encompassing gene expression in any and all cyanobacteria. *See In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970) (the first paragraph of § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification).<sup>22</sup> Accordingly,

22. The enablement rejection in this case was not based upon a post-filing date state of the art, as in *In re Hogan*, 559 F.2d 595, 605-07, 194 U.S.P.Q. 527, 536-38 (CCPA 1977). *See also United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1251, 9 U.S.P.Q.2d 1461, 1464 (Fed.Cir.1989) (citing *Hogan*); *Hormone*

*Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1568-69, 15 U.S.P.Q.2d 1039, 1047-48 (Fed.Cir.1990) (directing district court, *in remand*, to consider effect of *Hogan* and *United States Steel* on the enablement analysis of *Fisher*), *cert. dismissed*, — U.S. —, 111 S.Ct. 1434, 113 L.Ed.2d 485 (1991). We therefore do not

we affirm the § 112 rejection as to those claims.

[6] In so doing we do *not* imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology,<sup>23</sup> to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element. *See Fisher*, 427 F.2d at 839, 166 U.S.P.Q. at 24. In this case, we agree with the PTO that appellants' limited disclosure does not enable one of ordinary skill to make and use the invention as now recited in claims 1-46 and 50-51 without undue experimentation.

Remaining dependent claim 47 recites a cyanobacterium which expresses the chimeric gene of claim 1, wherein the cyanobacterium is selected from among the genera *Anacystis* and *Synechocystis*. Claim 48, which depends from claim 47, is limited to the cyanobacterium *Synechocystis* 6803. The PTO did not separately address these claims, nor indicate why they should be treated in the same manner as the claims encompassing all types of cyanobacteria.

consider the effect of *Hogan* and its progeny on *Fisher's* analysis of when an inventor should be allowed to "dominate the future patentable inventions of others." *Fisher*, 427 F.2d at 839, 166 U.S.P.Q. at 24.

Although these claims are not limited to expression of genes encoding particular *Bacillus* proteins, we note what appears to be an extensive understanding in the prior art of the numerous *Bacillus* proteins having toxicity to various insects. The rejection of claims 47-48 under § 112 will not be sustained.

## CONCLUSION

The rejection of claims 1-48 and 50-52 under 35 U.S.C. § 103 is *reversed*. The rejection of claims 1-46 and 50-51 under 35 U.S.C. § 112, first paragraph, is *affirmed* and the rejection of claims 47 and 48 thereunder is *reversed*.

AFFIRMED-IN-PART, REVERSED-IN-PART.

MAYER, Circuit Judge, dissenting.

An appeal is not a second opportunity to try a case or prosecute a patent application, and we should not allow parties to "undertake to retry the entire case on appeal." *Perini America, Inc. v. Paper Converting Machine Co.*, 832 F.2d 581, 584, 4 U.S.P.Q.2d 1621, 1624 (Fed.Cir.1987); *Eaton Corp. v. Appliance Valves Corp.*, 790 F.2d 874, 877, 229 U.S.P.Q. 668, 671 (Fed. Cir.1986). But that is precisely what the court has permitted here. The PTO conducted a thorough examination of the prior art surrounding this patent application and concluded the claims would have been obvious. The board's decision based on the examiner's answer which comprehensively explains the rejection is persuasive and shows how the evidence supports the legal conclusion that the claims would have been obvious. Yet, the court ignores all this and conducts its own examination, if you will, as though the examiner and board did not exist. Even if I thought this opinion were more persuasive than the board's, I could

23. The first paragraph of § 112 requires nothing more than *objective* enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971). How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is irrelevant. *Id.*

not join it because it misperceives the role of the court.

The scope and content of the prior art, the similarity between the prior art and the claims, the level of ordinary skill in the art, and what the prior art teaches are all questions of fact. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 693-94, 15 L.Ed.2d 545, 148 U.S.P.Q. 459, 467 (1966); *Jurgens v. McKasy*, 927 F.2d 1552, 1560, 18 U.S.P.Q.2d 1031, 1037 (Fed.Cir.1991). And "[w]here there are two permissible views of the evidence, the factfinder's choice between them cannot be clearly erroneous." *Anderson v. City of Bessemer City*, 470 U.S. 564, 574, 105 S.Ct. 1504, 1511-12, 84 L.Ed.2d 518 (1985). The mere denomination of obviousness as a question of law does not give the court license to decide the factual matters afresh and ignore the requirement that they be respected unless clearly erroneous. *In re Woodruff*, 919 F.2d 1575, 1577, 16 U.S.P.Q.2d 1934, 1935 (Fed.Cir.1990); *In re Kulling*, 897 F.2d 1147, 1149, 14 U.S.P.Q.2d 1056, 1057 (Fed. Cir.1990). There may be more than one way to look at the prior art, but on this record we are bound by the PTO's interpretation of the evidence because it is not clearly erroneous and its conclusion is unassailable. I would affirm on that basis.



LEVERNIER CONSTRUCTION,  
INC., Plaintiff-Appellee,

v.

The UNITED STATES, Defendant-  
Appellant.

No. 91-5058.

United States Court of Appeals,  
Federal Circuit.

Oct. 22, 1991.

Construction contractor sought attorney fees and expenses under the Equal

Access to Justice Act (EAJA) after settlement of equitable adjustment claim. On original hearing, the Claims Court, Reginald W. Gibson, J., 21 Cl.Ct. 683, granted application in part and denied it in part. Contractor sought reconsideration. The Claims Court, 22 Cl.Ct. 247, granted the motion, and held that contractor was entitled to recover additional amount representing consultant fees and expenses. Government appealed. The Court of Appeals, Bennett, Senior Circuit Judge, held that: (1) prosecution of equitable adjustment claim before contracting officer was not a "civil action" within meaning of the EAJA, and thus contractor was not entitled to recover consultant fees incurred in preparation of equitable adjustment claim; (2) Claims Court erred in applying 18% cost of living adjustment (COLA) to paralegal fees awarded under the EAJA; and (3) it was error to apply 18% (COLA) to hourly rates of attorneys whose time was claimed at \$75 an hour.

Reversed.

1. United States ⇐147(12)

Prosecution of equitable adjustment claim before contracting officer was not "civil action" within meaning of the Equal Access to Justice Act (EAJA), and thus contractor was not entitled to recover fees incurred by contract claim consultant for preparation of equitable adjustment claim. 28 U.S.C.A. § 2412.

See publication Words and Phrases for other judicial constructions and definitions.

2. United States ⇐147(5)

Equal Access to Justice Act (EAJA) is a waiver of sovereign immunity which must be strictly construed. 28 U.S.C.A. § 2412.

3. United States ⇐147(4)

In formulating an award of attorney fees under the Equal Access to Justice Act (EAJA), court may adjust statutory cap governing rate of attorney fees upward to account for an increase in cost of living. 28 U.S.C.A. § 2412(d)(2)(A)(ii).



that the mark PAN AMERICAN on toy trucks would falsely suggest a connection to the USOC or the Pan American games, and that the USOC did not prove that Toy Truck's intended use of this mark would be likely to cause confusion as to the source or sponsorship of the toy and model trucks. On these grounds the Board dismissed the USOC's opposition.

[1] It was improper for the Board to refuse to consider the 1998 enactment. The general rule is that a tribunal must apply the law as it exists at the time of the decision. *See Saint Francis College v. Al-Khazraji*, 481 U.S. 604, 608 (1987) ("The usual rule is that federal cases should be decided in accordance with the law existing at the time of decision.") Although this rule is subject to exceptions when justice requires, such as when vested rights are materially affected by the change in law, *Landgraf v. USI Film Prods.*, 511 U.S. 244, 265 (1994), no such reason has been proffered by Toy Truck Lines. Since this application was based solely on "intent to use," with no representation of actual use, there is no suggestion of the existence of any vested property right or investment in trademark use. *Cf. id.* at 270 (determination of statutory retroactivity requires consideration of "whether the new provision attaches new legal consequences to events completed before its enactment"). In this case there is no suggestion that application of the 1998 Act would impair any rights possessed before the enactment, increase Toy Truck's liability, or impose new duties for any past conduct. *See id.* at 280; *Lowry v. Secretary of Health and Human Services*, 189 F.3d 1378, 1380-81 (Fed. Cir. 1999). The Board was promptly advised of the new statute and its direct relationship to trademark use of "Pan American." The USOC's opposition to Toy Truck's application for registration could not be denied without consideration of the effect of the 1998 Act.

The unambiguous statutory language of § 220506(a)(4) reserves to the USOC the commercial use (other than "grandfathered" uses) of the disputed words PAN AMERICAN, without requiring any showing of likelihood of confusion or false connection. As the Court stated in *San Francisco Arts & Athletics, Inc. v. United States Olympic Comm.*, 483 U.S. 522, 531 [3 USPQ2d 1145] (1987) (concerning the Amateur Sports Act of 1978):

The protection granted to the USOC's use of the Olympic words and symbols differs from the normal trademark protection in two respects: the USOC need not prove that a contested use is likely to cause confusion, and an unauthorized user of the word does not have available the normal statutory defenses.

*Id.* at 531. Accordingly, the Board's findings that there is no likelihood of confusion or false suggestion of connection are irrelevant to the issue. It was incorrect for the Board to dismiss the USOC's opposition to Toy Truck's registration, for as a matter of law the USOC must prevail. We reverse the Board's dismissal of the USOC's opposition, and remand for further proceedings consistent with this decision.

No costs.

**REVERSED AND REMANDED**

## Ex parte Yamamoto

U.S. Patent and Trademark Office  
Board of Patent Appeals and Interferences

Appeal No. 97-1926

November 2, 2000

(Unpublished)

## PATENTS

### [1] Patentability/Validity — Obviousness — Evidence of (§ 115.0906)

Rejection of patent applicant's claims under 35 U.S.C. § 103 is reversed, since examiner has merely conjectured and speculated that, because prior art composition is directed to stabilized higher aliphatic aldehyde compounds, it would be considered by one of ordinary skill in art to be suitable for stabilization of claimed functional group containing compounds, and since such speculation is not sufficient for establishing prima facie case of obviousness.

Appeal from examiner's rejection of claims in patent application.

Patent application of Akira Yamamoto, Toyohisa Sakurada, and Ruichi Saguchi (se-



rial no. 07/978,036). Applicants appeal from final rejection, under 35 U.S.C. § 103, of all claims pending in application. Reversed.

[Editor's note: The Board of Patent Appeals and Interferences states that this opinion was not written for publication, and is not binding precedent of the board.]

James W. Badie, of Stoll, Miskin, Previto, Hoffman & Badie, New York, N.Y., for applicants.

Before Garris, Lieberman, and Tierney, administrative patent judges.

Lieberman, J.

### DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the decision of the examiner refusing to allow claims 1 through 3, which are all the claims pending in this application.

### THE INVENTION

The invention is directed to a method for the stabilization of a long-chain unsaturated aliphatic ester, alcohol, ketone or hydrocarbon compound having at least 10 carbon atoms and at least one double bond. The method requires admixing the compound with 2-(2'-hydroxy-5'-methylphenyl) benzotriazole and a phenolic compound. Each stabilizer is added in an amount of 0.1 to 10% by weight of the long-chain aliphatic unsaturated compound.

### THE CLAIM

Claim 1 is illustrative of appellants' invention and is reproduced below:

1. A method for the stabilization of a long-chain unsaturated aliphatic ester, alcohol, ketone or hydrocarbon compound having at least 10 carbon atoms and at least one double bond in a molecule, which comprises admixing the compound with 2-(2'-hydroxy-5'-methylphenyl) benzotriazole and a phenolic compound as an antioxidant each in an amount in the range from 0.1 to 10% by weight based on the amount of the long-chain aliphatic unsaturated compound.

### THE REFERENCE OF RECORD

As evidence of obviousness, the examiner relies upon the following reference.

Ishihara et al. 4,568,771 Feb. 4, 1986

### THE REJECTION

Claims 1 through 3 stand rejected under 35 U.S.C. § 103 as being unpatentable over Ishihara.

### OPINION

We agree with the appellants that the rejection under 35 U.S.C. § 103 is not well founded. Accordingly, we do not sustain this rejection.

#### *The Rejection under 35 U.S.C. § 103*

"[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability," whether on the grounds of anticipation or obviousness. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

We find that Ishihara discloses a method for stabilizing an aliphatic higher aldehyde compound by admixing the compound with a stabilizer selected from the group consisting of salicylic acid compounds and benzotriazole compounds among others. See column 2, lines 4-22. The stabilizing compounds are present in an amount of 0.01 to 10% by weight of the aldehyde compound. See column 2, lines 22-23. We find that among the compounds disclosed are 2-(2'-hydroxy-5'-methylphenyl) benzotriazole. See column 2, lines 66-67 and claim 1. We further find that among the compounds exemplified is BHT, i.e., Di-tert-butyl-p-cresol. See Tables 1 and 2.

The basic premise of the rejection is that although Ishihara differs from the claimed subject matter in disclosing the stabilization of a pheromone which just happens to be an aldehyde, one of ordinary skill in the art "having knowledge of the ability of the combination of BHT and a *hydroquinone compound* to protect an aldehyde pheromone from oxidation, would have sufficient motivation based on knowledge[d] [sic] of the nature of general oxidative reactions (as stated above) to use the same combination to protect pheromones having *other oxidative functional groups*." See Answer, pages 4 and 5. We disagree.

[1] This premise is not well taken because the examiner has not established by evidence or explanation that long-chain unsaturated aliphatic ester, alcohol, ketone or hydrocarbons are stabilized by the combination of stabilizers utilized by Ishihara of record, or that one of ordinary skill in the art would have had a

reasonable expectation that Ishihara's composition would be suitable for that use. The examiner has merely conjectured and speculated that because Ishihara's composition is directed to stabilized higher aliphatic aldehyde compounds it would be considered by one of ordinary skill in the art to be suitable for the stabilization of the claimed functional group containing compounds, and such speculation is not sufficient for establishing a *prima facie* case of obviousness. It is well settled that a rejection based on § 103 must rest upon a factual basis rather than conjecture, or speculation. "Where the legal conclusion [of obviousness] is not supported by the facts it cannot stand." *In re Warner*, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967); see also *In re Sporck*, 301 F.2d 686, 690, 133 USPQ 360, 364 (CCPA 1962). Accordingly, we reverse the rejection of claims 1 through 3.

### DECISION

The rejection of claims 1 through 3 under 35 U.S.C. § 103 as being unpatentable over Ishihara is reversed.

### REVERSED

## Microware Systems Corp. v. Apple Computer Inc.

U.S. Court of Appeals  
Eighth Circuit

No. 00-2006SI

Decided January 16, 2001

## TRADEMARKS AND UNFAIR TRADE PRACTICES

[1] Infringement; conflicts between marks  
— Likelihood of confusion — Particular marks — Confusion not likely (§ 335.0304.05)

Infringement; conflicts between marks  
— Defenses — Fair use (§ 335.1003)

Summary judgment was properly granted in favor of trademark infringement defendant who used "Mac OS 9" mark for its personal computers, since defendant's products and plaintiff's "OS-9" real-time operating systems are sold in different markets, since plaintiff

did not claim lost sales, and since defendant's mark accurately describes, in manner customary in industry, current version of defendant's product.

Appeal from the U.S. District Court for the Southern District of Iowa, Pratt, J.

Action by Microware Systems Corp. against Apple Computer Inc. for trademark infringement. Following denial of plaintiff's preliminary injunction motion and grant of summary judgment in favor of defendant, plaintiff appealed. Affirmed.

Deborah M. Tharnish, David Alan Tank, Daniel A. Rosenberg, and Kent A. Herink, of Davis & Brown, Des Moines, Iowa, for plaintiff-appellant.

George A. Riley, of O'Melveny & Myers, San Francisco, Calif.; Edmund J. Sease and Jeffrey D. Harty, of Zarley & McKee, Des Moines, for defendant-appellee.

Before Arnold, Fagg, and Bowman, circuit judges.

### Per curiam.

The plaintiff, Microware Systems Corporation, owns a registered trademark, "OS-9," on its software products, which are real-time operating systems. The defendant, Apple Computer, Inc., calls the current generation of its personal computer "MAC OS 9." Microware brought this suit for trademark infringement. The District Court<sup>1</sup> denied Microware's motion for a preliminary injunction and granted Apple's motion for summary judgment, holding as a matter of law that Apple had established the defense of fair use.

[1] We affirm. The evidence of confusion was minimal. Microware and Apple sold, for the most part, to entirely different markets. Microware does not claim it lost any sales. "MAC OS 9" accurately describes, in a fashion customary in the industry, the current version of Apple's product. For the rest, we refer the reader to the able district judge's full opinion, with which we agree in substance.

Affirmed.

<sup>1</sup> The Hon. Robert W. Pratt, United States District Judge for the Southern District of Iowa.

## **APPENDIX C**

**21 April 1994**  
**Vol. 368 Issue no. 6473**

◀ Superantigens are implicated in a number of diseases and in autoimmunity, so the understanding of their interactions with the immune system is of broad interest. The three-dimensional structure of a bacterial superantigen bound to a human class II histocompatibility complex molecule is reported on page 711. The antigen binds as an intact protein outside the 'normal' peptide antigen binding site of the class II MHC molecule.

## Electron rings

Electrides are crystalline salts containing alkali metal ions and trapped electrons to balance the metal's charge. Only four such compounds have so far been structurally characterized, number four being described on page 726. The new compound confirms that electrides are a varied group. A central six-oxygen crown ether is surrounded by six caesium cations, each one sandwiched between a further two crown ethers. The six 'balancing' electrons seem to be trapped in a puckered ring above and below the central molecule.

## Making comets

The spectacular disintegration of the Jupiter-bound comet Shoemaker-Levy 9 into about 20 fragments supports the view that cometary nuclei are piles of 'rubble' loosely held together by mutual gravitational attraction. How are these fragile structures formed in the outer Solar System? Processes involving either collisional coagulation in the solar nebula or gravitational collapse of a layer of dust particles have been proposed. Now Weldenschild shows that a two-stage process involving elements of both models provides a better explanation for the observed cometary structures. Pages 721 and 687. —

**LTP switch**

**Long-term potentiation (LTP) in the hippocampus is a popular model for the synaptic processes learning and memory. A new feature of LTP is reported on page 740, a 'switch' mechanism in which LTP is activated by metabotropic glutamate receptors.**

## Eye problem

The apparent complexity and sheer improbability of an organ as specialized as the vertebrate eye may seem to constitute a challenge to the mechanism of evolution. But new simulations suggest that a fish eye could have evolved step-by-step from flat skin in a mere 400,000 years. Page 690.

## Methane from the deep

Surface ocean waters are typically supersaturated with the greenhouse gas methane but the origin of the methane is unclear, mainly because methane producers need anaerobic environments but the surface water is well oxygenated. Karl and Tilbrook (page 732) offer a solution to this 'oceanic methane paradox', showing that methane produced by bacteria in the reducing environment provided by sinking particles of organic matter can produce the observed methane supersaturations.

## Kidney disorders

Renal cysts account for some 10% of kidney transplant dialysis patients, and effective treatments for the condition have proved elusive. But tests in an *in vitro* model for cyst formation and in a mouse model for congenital polycystic kidney disease show that taxol can inhibit cyst formation and prevent uraemic death. **Page 750.**

### Ecosystem threat

More evidence that the loss of biodiversity in the wake of human expansion has a deleterious effect on the continued survival of whole ecosystems. Naeem *et al.* reveal how experimental manipulation of biodiversity in closed, regulated ecological microcosms shows that biogeochemical processes in these systems can be increasingly altered or damaged by reduced biodiversity. Pages 734 and 686.

## Cancer causation

Cyclin-dependent kinase-4 inhibitor gene is identified as a likely candidate for the cytogenetic disruption of chromosome 9p21, which is associated with malignant melanomas, gliomas, lung cancers and leukaemias. In this issue, Nobori *et al.* report the positional cloning of this vulnerable gene which may inhibit cell proliferation in its normal guise. Page 753.

## Guide to Authors

Page 778.

**Nearly too late in Bosnia ■ Instant legislation unsatisfactory ■ Crisis of trust for US medical establishment**

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# Three-dimensional structure of a human class II histocompatibility molecule complexed with superantigen

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The structure of a bacterial superantigen, *Staphylococcus aureus* enterotoxin B, bound to a human class II histocompatibility complex molecule (HLA-DR1) has been determined by X-ray crystallography. The superantigen binds as an intact protein outside the conventional peptide antigen-binding site of the class II major histocompatibility complex (MHC) molecule. No large conformational changes occur upon complex formation in either the DR1 or the enterotoxin B molecules. The structure of the complex helps explain how different class II molecules and superantigens associate and suggests a model for ternary complex formation with the T-cell antigen receptor (TCR), in which unconventional TCR-MHC contacts are possible.

SUPERANTIGENS comprise a class of disease-associated, immunostimulatory molecules that bind class II MHC molecules and stimulate large numbers of T cells<sup>1,2</sup>. Members of the superantigen family include toxins from *S. aureus* and other bacteria<sup>3</sup>, as well as viral superantigens from mouse mammary tumour virus (MMTV)<sup>4</sup>. The *S. aureus* toxins are associated with food poisoning and toxic-shock syndrome, and the MMTV superantigen plays a critical role in viral transmission. The toxicity of bacterial superantigens is thought to be mediated by their potent T-cell-stimulating activities<sup>5</sup>, leading to lymphokine release<sup>6</sup>, respiratory distress and shock. Superantigens have also been implicated in rabies, rheumatoid arthritis, and mouse and human AIDS<sup>7</sup>.

The mechanism by which superantigens stimulate T cells differs from that of normal antigens. Conventional T-cell antigens are short proteolytic peptides from foreign proteins, bound in the peptide-binding groove of class I or class II MHC molecules<sup>8</sup>. The structures of both class I and class II MHC molecules<sup>9-11</sup> demonstrate that these bound peptides become an integral part of the MHC protein surface, which is displayed by antigen-presenting cells to specific T cells, generating an immune response. In contrast, bacterial superantigen activity is abolished by proteolysis and it is the intact superantigen protein that interacts with class II MHC molecules outside the peptide-binding groove<sup>12,13</sup> in order to stimulate T cells.

The interaction of conventional peptide antigens and superantigens with the T-cell antigen receptor (TCR) also differs. TCR molecules are structurally related to antibody molecules, with hypervariable regions forming a combining site for a specific peptide-MHC combination<sup>12</sup>. Superantigens bypass this specificity-determining region of the TCR, and interact with a surface of the TCR predicted to lie outside the antigen-combining site on the variable  $\beta$ -chain (V $\beta$ ) domain<sup>14-18</sup>. This ability

of superantigens to interact with both MHC and TCR molecules outside their normal antigen-specific sites leads to the stimulation of many more T cells than observed with normal peptide antigens.

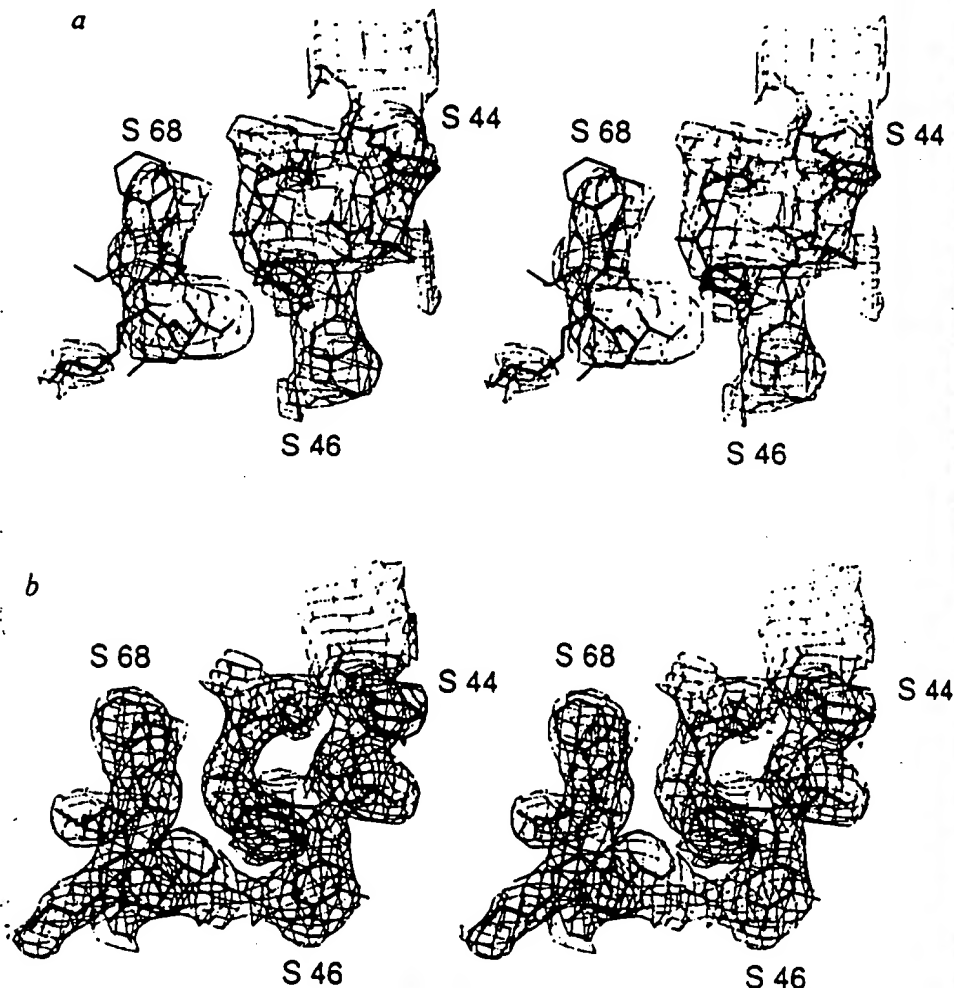
To understand better the molecular basis of the pathological effects of superantigens, we have determined the structure of a bacterial superantigen, *S. aureus* enterotoxin B (SEB), bound to a human class II MHC molecule, HLA-DR1, by X-ray crystallography. SEB binds outside the MHC peptide-binding site, with the N-terminal domain of SEB interacting with the DR1  $\alpha$ 1 domain. No large conformational changes are observed in either the class II molecule<sup>11</sup> or the SEB molecule<sup>19</sup> upon complex formation. SEB residues that affect the interaction with T-cell receptors are positioned to the side and above the DR1 peptide-binding site of the class II molecule, suggesting a model for the interaction of superantigen-MHC complexes with TCR, where normal TCR-MHC interactions are blocked.

## Structure determination

The structure of the DR1-SEB complex was determined using the data sets listed in Table 1, from two different DR1-SEB crystal forms. Initial electron density maps were generated using SIR/anomalous phases for crystal form I and improved by averaging with maps derived from HLA-DR1 crystals as described<sup>11</sup>. The initial model of the DR1 molecule was improved by cycles of building and refinement and a partial model for the SEB was built. A low-resolution data set of crystal form II (Table 1) was solved by molecular replacement with the partial model of the complex, and iterative non-crystallographic four-fold symmetry averaging was used (Fig. 1a) to obtain a polyalanine trace for 190 residues of the SEB molecule at low resolution. This model was used to calculate higher-resolution electron-density omit maps, followed by iterative non-crystallographic two-fold symmetry averaging, with data from crystal form I, and improved by further cycles of building and refinement (Fig. 1b).

|| To whom correspondence should be addressed.

FIG. 1 Electron density maps and temperature factors for the DR1-SEB complex. SEB electron density maps at the DR1-SEB interface. *a*, 15.0–4.3 Å [ $2F_o - F_{calc}$ ] map generated by 4-fold iterative averaging between crystal form I and form II. *b*, A current 2-fold averaged [ $2F_o - F_{calc}$ ] omit map at 2.7 Å resolution, calculated using current model phases and data from crystal form I, omitting the atoms shown. Both maps are contoured at  $1.0\sigma$  with a cover radius of 1.5 Å around the atoms shown. *c* and *d*, Top and side views (respectively) of the DR1-SEB complex showing the radial increase in temperature factor. Two DR1-SEB complexes are found in the asymmetric unit as shown. The current model is coloured by temperature factor (atomic *B*-factor), with blue representing *B*-factor values less than  $25 \text{ Å}^2$  and red representing *B*-factor values greater than  $100 \text{ Å}^2$  (see Table 1 for average SEB *B*-factors). Note the increase in *B*-factor as a function of distance from the DR1-SEB interface, and the correspondence with loops in the DR1 structure. The high-temperature factors may be due to SEB disorder within the crystal lattice. One SEB makes no contacts with other symmetry-related molecules in the lattice, whereas the other SEB molecule has only few crystal contacts in regions of the C-terminal domain that may not be accurately modelled. The DR1 molecules form crystal contacts in all lattice directions and may provide the predominant stabilization of the crystal lattice. The high-temperature factors may therefore also reflect a lower SEB occupancy within the lattice. Refinement of SEB occupancy before *B* refinement typically provides an improvement in  $R_{free}$  of 0.3–0.5%. Further experiments are necessary to resolve these possibilities.



The structure of the complex shows a gradient of disorder of the SEB molecules, extending radially out from the DR1-SEB interface (Fig. 1*c, d*). This has two consequences. First, five surface loops of the SEB molecules show no interpretable electron density, presumably because of the higher basal level of SEB disorder. Second, the SEB C-terminal domain shows generally weaker electron density, with stunted or absent side-chain density. The N-terminal domain of the SEB molecule, which forms most of the contacts to DR1 (Fig. 1*b*; and shown in yellow in Fig. 2*a*) is, however, the best ordered region of the SEB structure. The disorder evident in the structure does not affect either our major conclusions as to how SEB binds to class II MHC molecules or the implications for TCR interactions.

### Overview of DR1-SEB complex formation

Figure 2 shows top and stereo views of the DR1-SEB complex. SEB only contacts residues of the  $\alpha 1$  domain of DR1, interacting with amino acids from the first and third turns of the  $\beta$ -sheet and from the N-terminal region of the  $\alpha$ -helix. These residues form a deep, concave surface to one side of the peptide-binding site of DR1 (Fig. 3*c*), in agreement with mutational studies mapping the MHC-SEB interaction<sup>13</sup>. The potential influence of  $\alpha$ -chain polymorphisms in the binding of SEB to other human and mouse class II molecules is discussed later. SEB does not interact

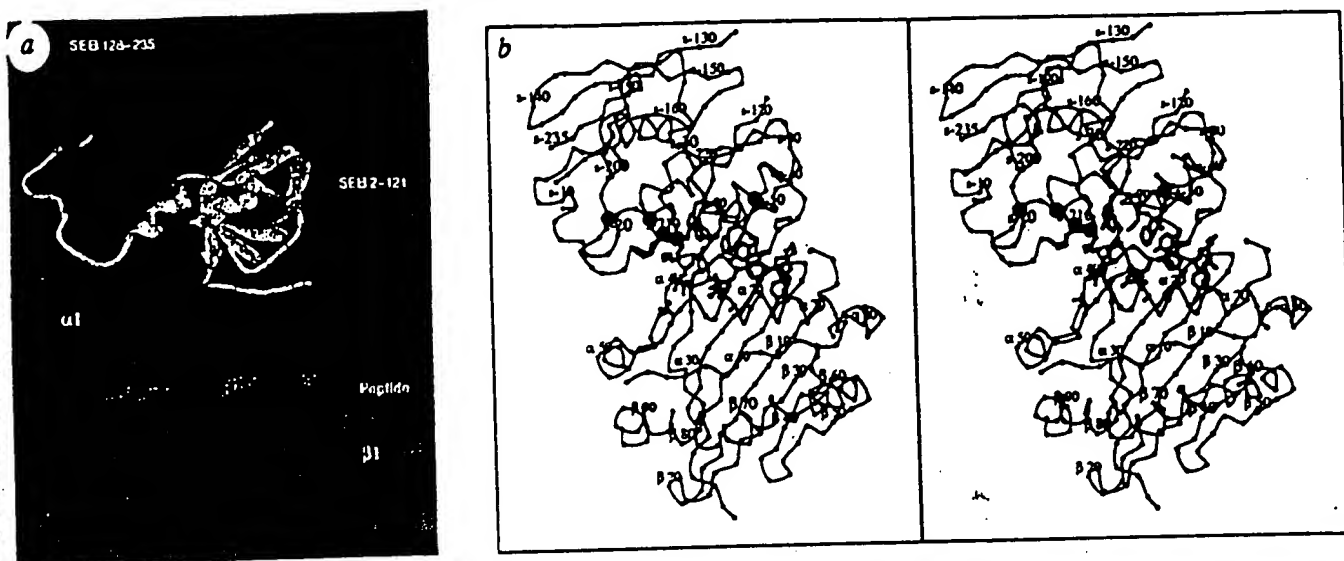


FIG. 2 Overview of the complex between HLA-DR1 and SEB. **a**, Top view, HLA-DR1  $\alpha 1$  and  $\beta 1$  domains are shown in blue;  $\alpha 2$  and  $\beta 2$  domains are not shown. N-terminal residues of SEB 2-121 are in yellow, and C-terminal residues 127-235 of SEB are in red; the peptide is shown in pink. The peptide conformation is based on fitting a polyalanine chain into the observed electron density corresponding to a mixture of self-peptides bound to the HLA-DR1 molecule. **b**,  $Ca$  trace of the complex (DR1  $\alpha 2$  and  $\beta 2$  not shown), showing all side chains involved in the DR1-SEB interface. SEB interface residues are in yellow; DR1 interface residues are in dark blue. Red spheres mark the SEB and SEA residues implicated in TCR interactions<sup>2,24,41-43</sup>.

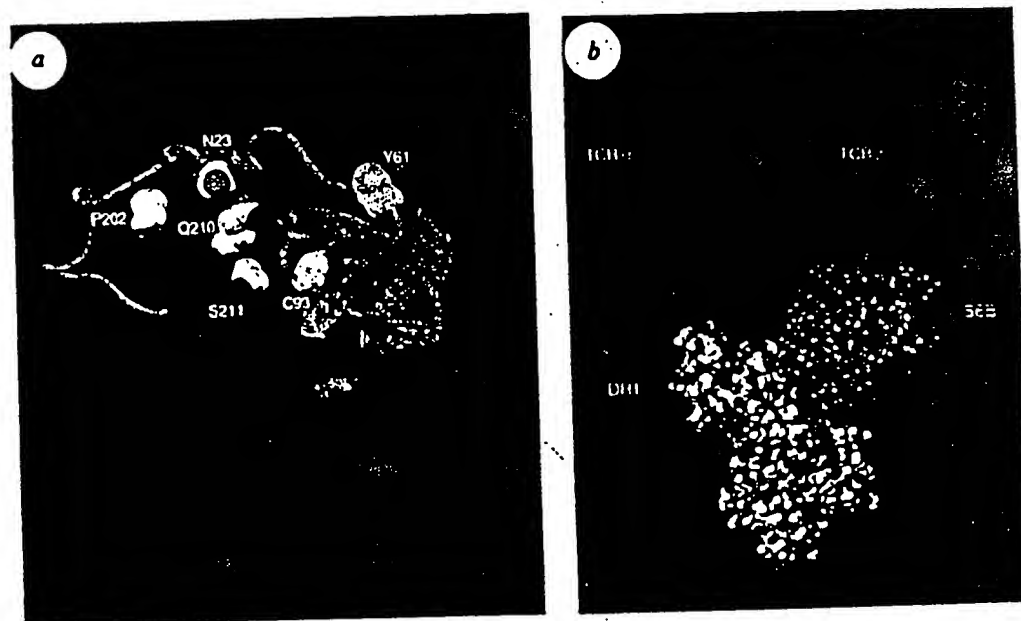


FIG. 3 Location of superantigen residues involved in TCR interactions and a model of ternary complex formation between DR1, SEB and TCR. **a**, Residues in SEB (N23, Y61, C93-C113; N60 not shown) and SEA (in SEA: G200, S206, N207; in SEB P202, Q210, S211) that have been implicated in TCR interactions by mutagenesis<sup>2,24,41-43</sup>. DR1  $\alpha 1$  and  $\beta 1$  domains are blue (DR1  $\alpha 2$  and  $\beta 2$  domains are not shown), SEB is yellow (N-terminal residues) and red (C-terminal residues), and peptide is pink. CPK representation is white for carbon atoms, red for oxygen, blue for nitrogen, and green for sulphur. **b**, Hypothetical model of ternary complex formation of DR1 and SEB with TCR. An immunoglobulin Fab fragment model of the TCR  $\alpha$ -chain in blue,  $\beta$ -chain in red. Hypervariable regions of TCR (CDR1, CDR2 and CDR3) are shown in yellow, and the HV4 loop and B strand of the  $V\beta$  domain are shown in white. DR1 carbon atoms are white, SEB carbon atoms are yellow, peptide carbon atoms are magenta. The view is looking down the DR1 peptide-binding site, with the DR1  $\beta$ -chain to the left and the  $\alpha$ -chain to the right. The TCR is positioned so that the SEB residues shown in **a** can interact with the white HV4 loop. **c**, Top view of the class II molecule, showing the region of the  $\alpha 1$  domain buried by complex formation with SEB. Surface of the DR1 molecule shown in magenta outside the SEB interaction area. Blue, hydrophobic surface buried by SEB; yellow, polar surface buried by SEB.



with class I MHC molecules and this region differs in class I and class II MHC structures<sup>11</sup>. Good peptide density is observed in the peptide-binding site, corresponding to a mixture of self-peptides, and has been modelled as polyalanine (Fig. 2). SEB does not interact directly with the peptide and the peptide conformation is very similar to that observed for a single peptide-DR1 complex<sup>20</sup>.

Residues from the SEB molecule that interact with DR1 derive predominantly from the smaller N-terminal  $\beta$ -barrel domain of the SEB molecule, although three residues from the C-terminal helix 5 (residues 210–217) also contact the DR1 molecule. Helix 5 is actually more closely associated with the N-terminal domain than with the C-terminal domain (Fig. 2b). The SEB residues most central to the interface lie in a turn between strands I

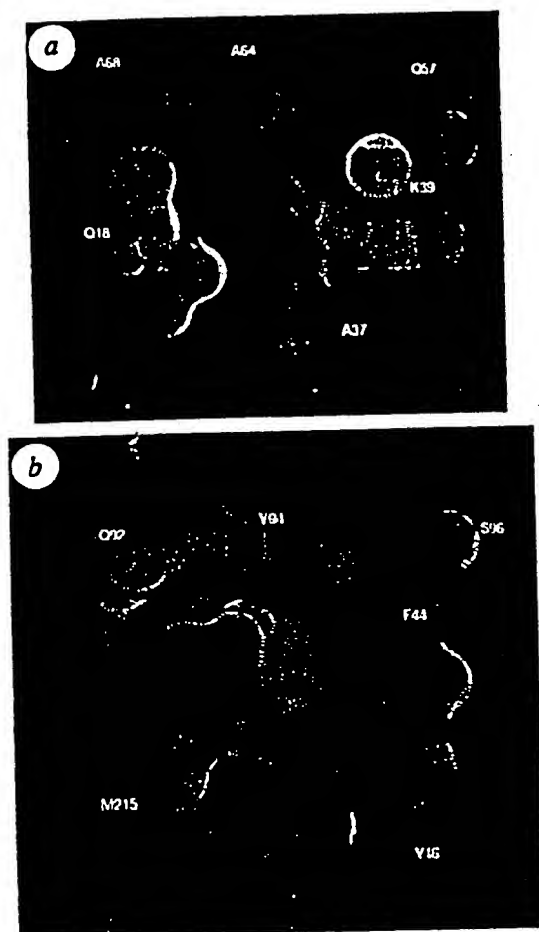
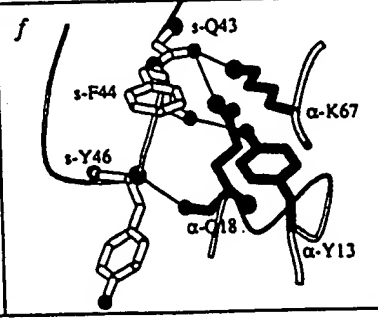
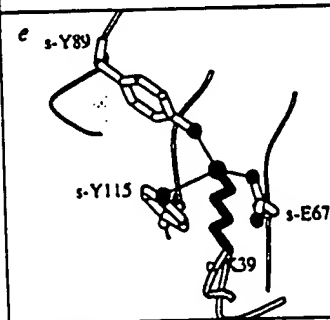
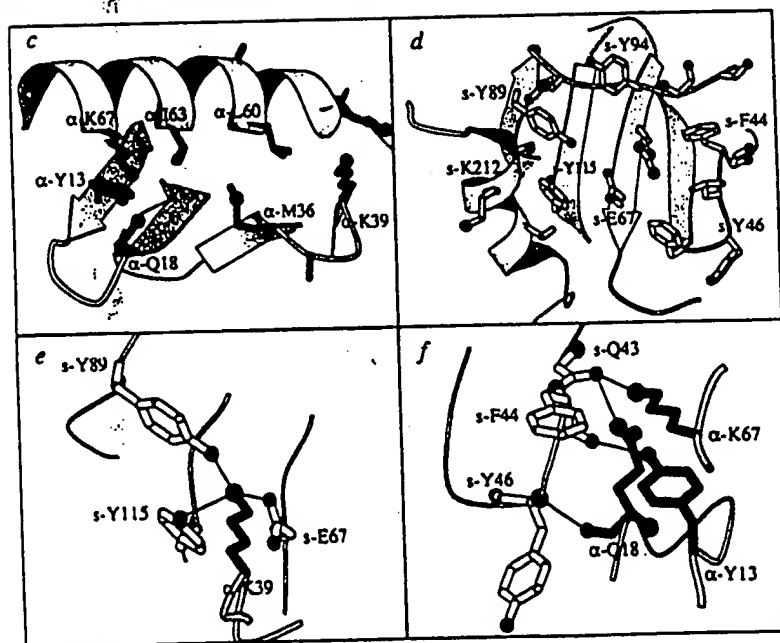


FIG. 4 The DR1-SEB binding interface. *a*, Surface view of the DR1 residues involved in binding to SEB. Yellow, polar atoms at surface; blue, hydrophobic atoms at surface. *b*, Surface view of the SEB residues involved in binding, same colour scheme as in *a*. *c*, DR1 residues involved complex formation, side view. DR1 residues are shown with blue bonds. Red, green and dark blue spheres represent oxygen, sulphur and nitrogen atoms, respectively. *d*, SEB residues involved in complex formation. SEB residues are shown with yellow bonds and atoms coloured as in *c*. *e*, Salt bridge formed between DR1  $\alpha$ -chain residue lysine 39 and SEB glutamic acid 67, with SEB tyrosines 89 and 115 forming hydrogen bonds. *f*, Potential hydrogen bonds formed between residues of the DR1 molecule and the main chain of residues 43–46 of the SEB molecule. Surfaces generated with MS<sup>23</sup> using a probe radius of 1.4 Å, and displayed in O<sup>24</sup>. *c–f* generated with Molscript<sup>25</sup>. Surfaces areas quoted in the text were calculated with the default atomic radii used by the program Access<sup>22</sup> and a probe radius of 1.4 Å.





(residues 33–39) and 2 (residues 48–52) and along strand 3 (residues 63–68). In addition, a stretch of residues in the SEB disulphide loop (residues 92–96) runs above the binding interface parallel to the DR1  $\alpha$ 1  $\alpha$ -helix. The C-terminal domain of the SEB molecule is oriented up and away from the class II molecule, consistent with the observation that N-terminal constructs containing residues 1–138 of the SEB molecule bind class II MHC molecules and retain partial activity<sup>21</sup>.

### Description of the Interface

Figure 2b shows a stereo view of the DR1 and SEB residues involved in complex formation. The interface is comparable in size to antigen–antibody interfaces, burying 780 Å<sup>2</sup> and 760 Å<sup>2</sup> of the DR1 and SEB solvent-accessible<sup>22</sup> surfaces respectively. Twenty-one residues of the DR1 molecule and nineteen residues from the SEB molecule are involved in complex formation.

A topological view of the binding interface shows a dramatic division of the complementary surfaces of the DR1 and SEB molecules. Figure 4a, b shows the molecular surfaces<sup>23</sup> of the DR1 and SEB molecules respectively, which are buried upon formation of the complex (coloured blue for non-polar atoms and yellow for polar atoms). Each binding surface is divided into two regions, one predominantly hydrophobic and one predominantly polar.

The hydrophobic region of the interface consists of a ridge of non-polar residues (F44, L45 and F47 (single-letter amino-acid code with residue number)) protruding from the loop between strands 1 and 2 of the SEB molecule (Fig. 4b, blue; and Fig. 4d), which fits into a predominantly hydrophobic depression on the DR1 molecule formed by residues of loops 1 and 3 and the  $\alpha$ -helix of the  $\alpha$ -chain (Fig. 4a, blue; Figs 3c and 4c). DR1 residues that contribute to this interaction include hydrophobic residues Y13, M36, A37, L60, I63 and A64, as well as the aliphatic portions of more polar residues such as Q18 (Fig. 4c). Mutations of residues F44 and L45 in the SEB molecule disrupt binding to class II MHC molecules<sup>24</sup>.

The polar region of the binding interface is more apparent on the SEB interaction surface, to the left of the hydrophobic ridge (Fig. 4b). This polar pocket on the SEB surface is complemented by a protrusion from loop 3 of the DR1 molecule formed by lysine 39 (Fig. 4a, e). This lysine forms a completely buried salt bridge with glutamic acid at position 67 of SEB, surrounded by hydrogen bonds from SEB Y89 and Y115 (Fig. 4e). The mutation of lysine 39 to alanine in the DR1 molecule reduces SEB binding<sup>40</sup>.

Three other residues of HLA-DR1 (Y13, Q18 and K67) are potentially involved in hydrogen bonds to the main chain of SEB residues 43–46 (Fig. 4f) and may be important in positioning the hydrophobic residues of the SEB molecule between the DR1 loops. As these residues vary between class II isotypes (Fig. 5), they may play a part in determining differences in the overall binding affinity.

In addition, SEB disulphide loop residues 92–96 contact the  $\alpha$ 1-domain  $\alpha$ -helix of the DR1 molecule along the upper face of the interaction region (Fig. 4d). In particular, SEB Y94 forms an extensive set of hydrophobic interactions with DR1 residues 60 and 61, whereas SEB S96 contacts DR1 residues 64, 67 and 68. Although these SEB residues do not bind into distinct pockets on the DR1 molecule, they have important implications for the accessibility of DR1 residues to TCR interactions (see below).

Two SEB residues (14 and 17) have been implicated in MHC binding<sup>24</sup>, but are not directly involved in the DR1–SEB interface and may have an indirect effect on MHC binding. This conclusion is supported by the observation that deletion of SEB residues 1–30 does not abrogate the ability of SEB to stimulate polyclonal T cells<sup>21</sup>.

### Other class II molecules and SEB

The binding affinity of SEB varies between different class II

MHC molecules. The ability of SEB to bind many different DR allotypes<sup>25</sup> can be explained by its exclusive interaction with the DR1  $\alpha$ -chain, which is conserved in all DR molecules. Binding to other class II isotypes is weaker than binding to DR<sup>26–29</sup> in the order DR > DQ > DP<sup>23,29</sup>, whereas for mouse alleles I–E binds SEB better than I–A<sup>29</sup>, but both bind more weakly than DR.

Figure 5a shows a plot of the surface of the DR1 molecule that is buried by the interaction with SEB, along with the corresponding residues that are found in other human (DP/DQ) and mouse (I–A/I–E) alleles. For the human class II isotypes DP and DQ, about 50% of the residues in the DR1–SEB interface are conserved, although the subset of these residues differs between DP and DQ. Lysine 39 is found in all three isotypes, indicating that a salt bridge with E67 of SEB could be formed (Fig. 4e). Many of the residues that form the hydrophobic portion of the interaction surface (Fig. 4c, and shown in blue in Fig. 4a) are conserved (L60, A64) or conservatively substituted (M36 to L, I63 to I or M).

Although a number of residue differences could account for a lower binding affinity for DQ and DP, relative to DR, the substitution of Q18 to proline in both DQ and DP is particularly central to the DR1–SEB interface. Proline would disrupt one hydrogen bond (Fig. 4e), and would potentially alter the conformation of the other residues in this loop. DP molecules have additional mutations in residues in this region (Y13 to valine and K67 to asparagine) that form one side of the SEB binding site (Figs 3c and 4a, b), which could further destabilize the interaction with SEB molecules.

In the case of the mouse class II molecules, 12 of 17 residues are conserved in I–E molecules and 10 of 17 in I–A molecules. I–E molecules have a lysine-to-serine mutation at position 39, which would abolish the salt bridge with SEB (Figs 4e and 5a). Serine may partially compensate for the lost salt-bridge interaction. Further mutational studies are needed to define the function of different amino acids at the interface.

### Other superantigens and class II molecules

Although the sequence similarity of different *S. aureus* toxins with SEB ranges from 40 to 90%, there is evidence for distinct MHC binding sites for different toxins<sup>28,30,31</sup>. Binding of *S. aureus* enterotoxin A (SEA) has been mapped to the MHC class II  $\beta$ 1 domain<sup>32,33</sup>; binding of toxic-shock-syndrome toxin TSST-1 has been shown to be sensitive to both  $\alpha$ 1 and  $\beta$ 1 domains<sup>34–36</sup>. A comparison of the SEB residues involved in binding to DR1 with the corresponding residues in SEA and TSST-1 provides some insight into the functional data available for these toxins.

Figure 5b shows a plot of the buried surface area of the SEB residues involved in binding DR1, with the corresponding residues from other *S. aureus* toxins. Of the DR1–SEB interactions described above, a number of central residues are conserved or conservatively substituted in SEA, including F44, L45, D67, Y89 and Y115. The conservation of these residues suggests that SEA may bind to class II molecules in a similar way to SEB. Substitution of the amino acids corresponding to SEB residues F44 and L45 in SEA (F47, L48) reduces its T-cell-stimulatory activity<sup>37</sup> and substitution of SEA L48 reduces MHC binding but does not abolish it (J. Kappler, personal communication). Other interactions discussed below may contribute to additional SEA binding.

Figure 5b shows that the major features of the SEB-binding interface are absent in TSST-1, based on a structural alignment of the two proteins<sup>38,39</sup>. These changes include the loss of the hydrophobic ridge (F44 to S) and the residues that interact with DR1 K39 (SEB E67 to I, Y89 to T, Y115 to I). Mutation of  $\alpha$ -chain residues M36 to I, or K39 to S, abolishes TSST-1 binding to HLA-DR7 (ref. 35). Both of these residues are directly involved in the DR1–SEB binding interface (Fig. 4) and mutation of K39 to A disrupts SEB binding as well as TSST-1

binding<sup>40</sup>. This indicates that although SEB and TSST-I are sensitive to mutations in the same region of the class II  $\alpha$ -chain, their specific interactions may be substantially different.

### Superantigen residues interacting with TCR

Some mutations in the SEB molecule affect T-cell stimulation, but not class II binding, suggesting specific contacts with the TCR<sup>24</sup>. These residues are shown in Figure 3a, together with residues that determine V $\beta$  specificity between enterotoxins SEA and SEE<sup>21,41</sup>. The SEA residues are in the C-terminal domain of the superantigen structure, in a loop between strand 9 and helix 5 of SEB. Mutation of the cysteine residues involved in the disulphide bond in SEA<sup>43</sup> and SEB<sup>24</sup> also prevents T-cell stimulation. All of these residues line a region between the two domains of the superantigen, defining a potential TCR-binding site that is located above and to one side of the MHC peptide-binding groove (Fig. 3a).

### Implications for ternary complex with TCR

The hypervariable region 4 (HV4) of the V $\beta$  domain of the TCR is important for superantigen interactions<sup>14-18</sup>. In a hypothetical model of the TCR<sup>44</sup>, this region lies on an exposed face of the V $\beta$  domain (shown in white in Fig. 3b). Direct binding studies with a soluble TCR  $\beta$ -chain<sup>45</sup> indicate that these interactions may be sufficient for formation of an MHC-superantigen-TCR complex.

The juxtaposition of the HV4 region of the TCR with the superantigen residues involved in TCR interactions leads to a model with interesting implications for the formation of the ternary complex between MHC, SEB and TCR (Fig. 3b). The complementarity-determining regions (CDRs) of the TCR are oriented over the MHC peptide-binding site, with the V $\beta$  domain bound to SEB and the V $\alpha$  domain above the class II  $\beta$ 1 domain. This model is consistent with a role for the TCR  $\alpha$ -chain and MHC polymorphism in modulating super-

TABLE 1 Data collection and refinement statistics

Data	Cell dimensions (Å)	Resolution (Å)	$R_{\text{sym}}$ (%) <sup>a</sup>	Completeness (%)		
Crystal form I, space group $P2_12_12_1$						
Native	95.0 × 114.7 × 149.8	30.0–2.7	5.7	86		
Synchrotron		2.8–2.7	32.1	87		
Crystal form II, space group $P2_12_12_1$						
Native	95.8 × 127.0 × 183.8	30.0–4.35	11.4	82		
GX-13		4.69–4.35	31.0	63		
Refinement statistics						
Resolution (Å)	No. of reflections (working set)	No. of atoms†	R.m.s. bonds (Å)‡	R.m.s. angles‡	$R_{\text{cryst}}$ (%)§	$R_{\text{free}}$ (%)
6.0–2.7	31,557	9,400	0.017	2.16	25.7	32.7

A papain-solubilized form of the human class II MHC molecule, HLA-DR1 (DRA, DRB1#0101)<sup>46</sup> was co-crystallized with SEB in a 1:1 molar ratio (final total protein concentration, 15 mg ml<sup>-1</sup>) from a stock solution in 10 mM Tris buffer, pH 7.5. Crystals were grown by vapour diffusion, by mixing 2  $\mu$ l protein solution with 2  $\mu$ l well solution containing 10 mM sodium acetate, pH 4.7, 10% ethylene glycol, and 12–20% PEG4000 (Fluka), at 25 °C. SEB was obtained as a lyophilized powder from Sigma, or Toxin Technology, from culture supernatants of an SEB-producing strain of *S. aureus* (Toxin Technology) and as a kind gift from M. Sax. Two crystal forms grew under the same conditions. Data for crystal form I were collected from crystals flash-frozen at –165 °C. Data for crystal form II were collected from 8 crystals at 25 °C and merged using the Buddha<sup>47</sup> and CCP4 programs<sup>48</sup>. Data were collected using a Nicolet/Xentronics area detector and Elliot GX-13 rotating-anode X-ray source with Franks double-mirror optics, and also at the Cornell High Energy Synchrotron Source (CHESS) F-1 beamline, using Kodak phosphor-image plates. CHESS data were processed with Denzo and Scalepack (Z. Otwinowski, personal communication). DR1-SEB SIR/anomalous phased electron density maps were iteratively averaged with DR1-SIR electron density maps and a model of the HLA-DR1 molecule was built as described<sup>11</sup>. The SEB region was not easily interpretable, so the DR1 model was improved, first by building into single DR1 domain omit maps, comparing maps calculated with both model and experimental SIR/anomalous phases, and maps calculated with DR1 model phases. Cycles of building and refinement of the DR1 model improved the SEB regions and a partial polyaniline model of SEB was built. This partial model of the DR1-SEB structure was used to solve the second, low-resolution DR1:SEB crystal form by molecular replacement using the Navazsa suite of programs<sup>49</sup>, giving an initial R-factor of 40.5% and a correlation coefficient of 48.4% from 8–4.3 Å. Iterative four-fold real-space averaging between the two space groups was carried out using the Bragg package of programs<sup>50</sup>, generating the electron density map shown in Fig. 1a. A 190-residue polyaniline trace of SEB was built and used to phase five higher-resolution (3.5 Å) maps, where 20% of the SEB polyaniline trace was omitted. Side chains were built into interpretable electron density, and the model was improved by further cycles of building, refinement and iterative two-fold non-crystallographic real-space averaging. The resolution was gradually extended from 3.5 to 2.7 Å. At all stages, refinement paths were taken that minimized the free R-factor<sup>51</sup>. As refinement proceeded, a number of loops in the SEB structure remained untraceable. These loops include residues 57–60 and 99–110 of the first domain and residues 122–126, 176–182, and the N- and C-terminal residues 1 and 236–239 of the second domain. In addition, three regions in the C-terminal domain of SEB do not show unambiguous side-chain density, including the N-terminal SEB region (residues 1–11)  $\beta$ -strands 6 and 7 (residues 127–154), and the C-terminal region of helix 4 and the adjacent loop residues (residues 169–175). In general, density for the second domain is less well defined. Refinement shows a dramatic difference in average atomic B-factor values between the HLA-DR1 molecule and the SEB molecule. The average Ca B-factor is 30 Å<sup>2</sup> for DR1, 55 Å<sup>2</sup> for the N-terminal domain of SEB1 (SEB1 is one of the SEB molecules in the asymmetric unit), and 70–80 Å<sup>2</sup> for the C-terminal domain, showing a radial increase from the DR1-SEB interface (Fig. 1). Given the high temperature factors for SEB, it was important to verify the SEB model. An independently refined model of HLA-DR1 (ref. 20), with no phase bias for the SEB model, was used to calculate  $|2F_{\text{obs}} - F_{\text{calc}}|$  averaged and unaveraged omit maps. The omit maps verified the overall placement of the SEB molecule in the map, indicating a deteriorating map quality for SEB regions in the following order: N-terminal domain (SEB1) > C-terminal domain (SEB1) ~ N-terminal domain (SEB2) > C-terminal domain (SEB2), where SEB1 and SEB2 refer to the two SEB molecules in the asymmetric unit. In the final stages, the independently determined structure of the SEC3 molecule was compared to the SEB model, leading to rebuilding of difficult regions of the SEB, including three loops (29–32, 201–203 and 224–229), the N-terminal strand (residues 2–13), and the C-terminal residues of helix 4 and the adjacent loop (157–175). Fewer than 5% of the  $\phi/\psi$  angles lie outside allowed regions of a Ramachandran plot.

<sup>a</sup>  $R_{\text{sym}} = \sum || - \langle I \rangle| / \sum I$ , where  $I$  is the observed intensity, and  $\langle I \rangle$  is the average intensity from several measurements.

† 9,400 non-hydrogen atoms represents 93% of the expected atoms for the DR1-SEB complex. Water molecules have not yet been included in this refinement.

‡ R.m.s. bond angles and lengths are r.m.s. deviations from ideal values.

§ R-factor calculated with working set reflections greater than  $2\sigma$ .

|| R-factor calculated with 3,383 reflections removed before automated refinement and greater than  $2\sigma$ .

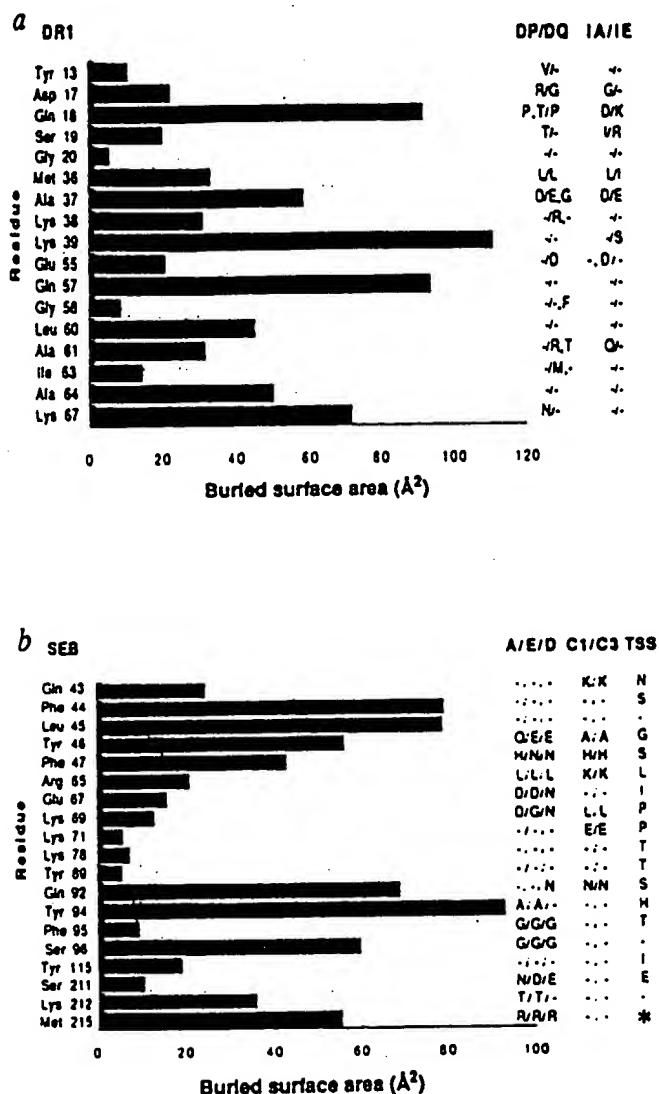


FIG. 5 Residues involved in the DR1-SEB interaction vary between class II isotypes and related superantigens. *a*, Plot of the buried solvent-accessible surface area<sup>22</sup> for each residue of the HLA-DR1 molecule involved in SEB binding. Corresponding residues in HLA-DP, HLA-DQ, mouse I-A, and I-E molecules is indicated to the right of the plot. *b*, Plot of the buried solvent-accessible surface area for each residue of the SEB molecule involved in HLA-DR1 binding. Corresponding residues in related superantigens are listed to the right for SEA, SED, SEE, SEC1, SEC3 and TSST-1. The TSST-1 residue alignment is based on the structural alignment of TSST-1 and SEB<sup>28,30</sup>. Surface areas were calculated with the program Access<sup>22</sup> as described in Fig. 4 legend. A dash is used for residues identical to DR1 or SEB and an asterisk indicates a deletion.

antigen stimulation through direct TCR-MHC interactions<sup>16,24,26,29,46-53</sup>.

However, the DR1-SEB complex suggests that the interactions between TCR and MHC molecules during superantigen stimulation differ from the interactions involved in antigenic peptide stimulation. Residues of the DR1  $\alpha$ 1-domain  $\alpha$ -helix that are usually exposed and might interact with the TCR are partially or completely buried in the complex by SEB residues 92-96 (Fig. 3c). These MHC surface residues (at positions 55, 57, 58, 60, 61, 63, 64, 67) influence T-cell stimulation when mutated<sup>12,13</sup>, indicating that this region of the DR  $\alpha$ 1-domain  $\alpha$ -helix is important for TCR recognition of peptide antigens and arguing for an unconventional mode of interaction between TCR and MHC during superantigen stimulation.

## Discussion

The crystal structure of the DR1-SEB complex shows that SEB binds to the  $\alpha$ 1 domain of class II molecules, positioning a TCR-binding site above and to the side of the MHC peptide-binding site. Antigenic peptides are not inhibitors of SEB stimulation<sup>13</sup> and the structure demonstrates that peptides and SEB occupy two distinct regions of the class II MHC molecule. In the DR1-SEB crystal, electron density is observed for 13 residues of an extended peptide chain, corresponding to a mixture of self peptides bound to DR1 (T.S.J., manuscript in preparation). The

details of the DR1-SEB interaction indicate how superantigen affinity could be modulated for different class II isotypes.

The interaction of related bacterial superantigens with class II molecules may differ from that seen in the DR1-SEB structure. Two lines of evidence support such a view. The first is that different superantigens do not all cross-compete in binding studies. SEB and TSST-1 do not competitively inhibit each other or completely block SEA binding to HLA-DR<sup>28,30,31</sup>, indicating the existence of independent binding sites. However, SEA is able to compete effectively with both SEB and TSST-1 for binding<sup>31</sup>, suggesting that these sites may overlap. In addition, mutational studies of HLA-DR and SEA suggest that SEA has a different binding site. Histidine 81 of the class II  $\beta$ -chain<sup>32,33</sup> is important for SEA binding to DR, but has no effect on SEB or TSST-1 binding. This interaction may be mediated by a zinc atom bound to a metal coordination site found in SEA, SED and SEE<sup>34</sup>. SEB does not require zinc to bind class II molecules, and the residues in SEA that bind zinc are in the C-terminal domain, far from the DR1-SEB interface, indicating that SEA has a different mode of binding from SEB.

Important features of the DR1-SEB interaction are conserved in SEA, suggesting that SEA may have evolved two distinct modes of binding to class II molecules, one similar to SEB and another zinc-mediated interaction with the class II  $\beta$ -chain. This is consistent with the available mutational and binding data.

Binding of one SEA molecule to both  $\alpha$ -chain and  $\beta$ -chain sites on one class II molecule is unlikely, considering the DR1-SEB structure, the competition data, and the zinc-binding site of SEA. However, one SEA molecule could potentially crosslink two class II molecules, with the N-terminal domain interacting with the  $\alpha$ 1 domain of class II (as observed for SEB) and the C-terminal domain interacting with the  $\beta$ -chain of another class II molecule. This type of crosslinking might explain the ability of these superantigens to stimulate T cells at concentrations well below their measured  $K_d$  values.

The crystal structure also supports a model of ternary complex formation in which the MHC interaction with the TCR is distinct from the peptide-mediated interaction. A stretch of residues located in the SEB disulphide loop lies across the  $\alpha$ 1  $\alpha$ -helix of DR1, covering residues that have been implicated in TCR recognition of peptide-MHC complexes. This suggests that superantigens may not take advantage of any residual affinity of TCR for MHC derived from positive selection during thymic education. However, the location of SEB residues that interact with TCR and of TCR residues that interact with superantigens

suggests that the TCR may still be positioned in close proximity to the class II peptide-binding site. This may explain how TCR  $\alpha$ -chains and MHC polymorphisms can modulate superantigen stimulation. Superantigens may have evolved to bind class II MHC molecules, not in order to use existing MHC-TCR interactions to stimulate T cells, but rather to take advantage of additional signals and organization inherent in conventional antigen presentation.

Superantigens have been directly implicated in a number of diseases and it has been suggested that they might be involved in the generation of autoimmunity<sup>35</sup> by stimulating existing autoreactive T cells. It has been shown that SEB can induce relapsing paralysis in mice that have previously been immunized with a peptide that induces experimental autoimmune encephalomyelitis<sup>36,37</sup>. This indicates that the powerful T-cell-activation properties of superantigens may be important in the development and relapse of autoimmune disorders. An understanding of the structural requirements for the action of these superantigens may further the development of strategies to control the onset and progression of disease. □

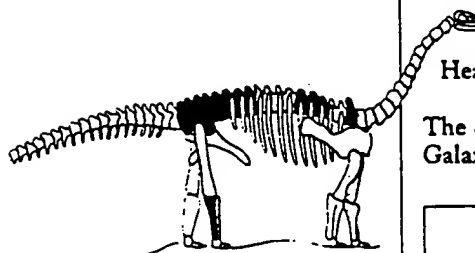
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**1803 & 1865**  
Herpes link to Kaposi's?



**1805**  
It could be a  
contender

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# Toxic Shock Syndrome Toxin-1 Complexed with a Class II Major Histocompatibility Molecule HLA-DR1

Jongsun Kim, Robert G. Urban, Jack L. Strominger, Don C. Wiley\*

The three-dimensional structure of a *Staphylococcus aureus* superantigen, toxic shock syndrome toxin-1 (TSST-1), complexed with a human class II major histocompatibility molecule (DR1), was determined by x-ray crystallography. The TSST-1 binding site on DR1 overlaps that of the superantigen *S. aureus* enterotoxin B (SEB), but the two binding modes differ. Whereas SEB binds primarily off one edge of the peptide binding site of DR1, TSST-1 extends over almost one-half of the binding site and contacts both the flanking  $\alpha$  helices of the histocompatibility antigen and the bound peptide. This difference suggests that the T cell receptor (TCR) would bind to TSST-1:DR1 very differently than to DR1:peptide or SEB:DR1. It also suggests that TSST-1 binding may be dependent on the peptide, though less so than TCR binding, providing a possible explanation for the inability of TSST-1 to competitively block SEB binding to all DR1 molecules on cells (even though the binding sites of TSST-1 and SEB on DR1 overlap almost completely) and suggesting the possibility that T cell activation by superantigen could be directed by peptide antigen.

Toxic shock syndrome toxin-1 (TSST-1) is a 22-kD protein superantigen secreted by *S. aureus* that causes toxic shock in humans probably by polyclonal activation and lymphokine secretion from T cells (1). Patients exhibit selective expansion of T cells (up to 50% of the total) expressing the  $V_{\beta}2$  family of TCR  $\beta$  chains (2). Like other bacterial and viral superantigens, TSST-1 cross-links the class II major histocompatibility complex (MHC) proteins of antigen-presenting cells to the  $V_{\beta}$  chains of the antigen receptor of T cells (3). Earlier studies indicate that superantigens bind primarily outside of the peptide-antigen binding groove of class II MHC molecules and to mainly conserved regions of TCRs, including a fourth region of hypervariability (CDR4) on  $V_{\beta}$  chains (2, 4). Furthermore, bacterial superantigens function as intact molecules, unlike conventional antigens, which are degraded to a short peptide and complexed with an MHC molecule for recognition by T cells (5). Their binding mode may circumvent the clonal specificity of T cells by binding away from the six major TCR hypervariable loops, enabling superantigens to activate a large fraction of all T cells (10 to 30%, hence their name) that bear certain families of TCR  $V_{\beta}$  chains (6).

The x-ray crystal structure of a complex between the superantigen *S. aureus* entero-

toxin B (SEB) and the human class II MHC molecule HLA-DR1 was determined recently (7). It revealed that SEB binds ex-

clusively to the  $\alpha$  chain of DR1 off one edge of the peptide binding groove. One loop of SEB covers residues of DR1 recognized by the TCR during conventional antigen recognition (8), which suggests an unconventional model for the interaction between the TCR and MHC during superantigen activation (7). Although they are only 16% identical in sequence (9), TSST-1 and SEB have very similar three-dimensional structures (9, 10). However, sequence differences in TSST-1 at residues corresponding to SEB residues involved in binding to DR1 suggest the existence of substantially different superantigen-DR1 interactions (7), although mutation and competition studies suggest substantial overlap in the binding site on DR1 (11-15).

Here, we determined the three-dimensional structure of the TSST-1:DR1 complex by x-ray crystallography. The locations of the DR1 and TSST-1 molecules in a crystal of the TSST-1:DR1 complex were both determined by two independent methods with the use of coordinates of the individual molecules (9, 16). First, their locations were each found by separate, six-dimensional searches of  $\alpha$  carbon models (17) through a single isomorphous re-

**Table 1.** Data processing and refinement statistics. HLA-DR1 (27) was cocrystallized with TSST-1 in a 1:1 molar ratio (final total protein concentration of ~12 mg/ml, 10 mM Tris buffer, pH 7.5). Crystals of lyophilized TSST-1 (Sigma or Toxin Technology) grown by vapor diffusion from 100 mM acetate (pH 5.5), 17% polyethylene glycol (4 kD), and 5% ethylene glycol (or methyl-propanediol) at room temperature have space group  $I4_1$ , with unit cell dimensions of  $a = b = 144.08$  Å and  $c = 106.55$  Å. Diffraction data to 3.5 Å resolution from a native crystal and from one heavy atom derivative [soaked in 3 mM ethylmercury-thiosalicylate (EMTS) solution for 3 hours] were collected at room temperature with the use of an MAR-research detector with  $\text{CuK}\alpha$  x-rays generated by an Elliot GX-13 rotating anode with Franks double mirror optics. Data were processed and scaled with the program XDS (28). The heavy atom position was determined from difference Patterson maps and was confirmed by difference Fourier analysis with the molecular replacement phases calculated from either the DR1 molecule alone or the TSST-1 molecule alone with the use of the program ROCKS (29). The heavy atom binding site is common to that of other DR1 crystal forms (7, 16). Heavy atom parameters were refined and single isomorphous replacement (SIR) phases calculated with the program PHARE. SIR phases were improved by solvent flattening (30) (50% solvent) to give a 3.5 Å electron density map in which DR1 and TSST-1 were located by a six-dimensional real space search (17). DR1 and TSST-1 locations were revealed as peaks nine and five times, respectively, the standard deviation in independent, six-dimensional search functions. DR1 and TSST-1 positions were also independently determined by molecular replacement methods with the use of the program package X-PLOR (18). The correlation coefficients calculated for the highest peaks in the DR1 and TSST-1 rotation functions were 0.11 and 0.10, both twofold greater than the next highest peaks. The translation function values were 0.22 and 0.31, respectively, with standard deviations of 0.012.  $R$  factors calculated from DR1 or TSST-1 alone were 49.7 and 48.6%, respectively. The relative locations of the DR1 and TSST-1 molecules along the crystallographic  $z$  axis were determined by inspection of the heavy atom binding sites determined by difference Fourier analysis with the use of either DR1 model phases or TSST-1 model phases. The  $R$  factor for the TSST-1:DR1 complex thus located was 43%. The location of DR1 and TSST-1 determined by molecular replacement and independently by the six-dimensional search of the SIR map were the same, revealing one TSST-1:DR1 complex per asymmetric unit. A further indication that the location of DR1 was correct was the discovery in this crystal of the same dimer of DR1 molecules seen in three earlier crystals containing DR1 (7, 16), this time positioned on a crystallographic twofold symmetry axis.  $I_{\text{obs}}$ , heavy atom structure factor;  $E$ , residual lack of closure; FOM, mean figure of merit; rms, root mean square.

Data set	Resolution (Å)	Data coverage (%)	$R_{\text{merge}}^*$ (%)	$R_{\text{iso}}^\dagger$ (%)	FOM	rms $I_{\text{obs}}/E$
Native	3.5 (3.7 to 3.5)	92.2 (92.8)	10.8 (27.8)			
Derivative	3.5 (3.7 to 3.5)	95.5 (98.3)	12.9 (32.8)	20.0	0.40	1.51

\* $R_{\text{merge}} = \sum_i \sum_j |I_{\text{obs}} - \langle I_{\text{obs}} \rangle| / \sum_i \sum_j I_{\text{obs}}$  where  $I_{\text{obs}}$  is the observed intensity.  $\dagger R_{\text{iso}} = \sum_i |F_{\text{native}} - F_{\text{derivative}}| / \sum_i F_{\text{native}}$ .

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placement, solvent-flattened 3.5 Å electron density map. The same locations were found by independent rotation and translation function calculations (18) for each protein in the TSST-1:DR1 crystal (Table 1).

The current model contains 94% of the residues of DR1, 13 alanine residues representing antigenic peptides bound to DR1, and the entire 194 amino acids of TSST-1. (Residue numbers are prefixed with  $\alpha$  and  $\beta$  to indicate the  $\alpha$  and  $\beta$  subunits of the DR1 molecule, and p and t to indicate the anti-

genic peptide bound on DR1 and TSST-1, respectively.) The model is presently refined to a crystallographic R factor of 0.22 (10 to 3.5 Å,  $R_{\text{free}} = 35\%$ ) (Table 2). Because significant intensity data were unmeasurable beyond 3.5 Å resolution, high-resolution details, such as the certainty of hydrogen bonding or salt bridge formation, which require a high-resolution refined structure, cannot be reliably assessed from the current model. However, a series of simulated annealing omit maps calculated

around the contact regions clearly shows that the location of side chains and the composition of the interfaces in the TSST-1:DR1 complex are evident. DR1 crystallizes as a dimer of the  $\alpha\beta$  heterodimer, as has been observed in other DR1 crystal forms (7, 16).

The overall structure of the TSST-1:DR1 complex is shown in Fig. 1. The  $\text{NH}_2$ -terminal  $\beta$  barrel domain of TSST-1 is primarily involved in complex formation between DR1 and TSST-1 molecules, as had been suggested by x-ray crystallographic analysis of TSST-1 (9, 10) and peptide studies mapping the TSST-1:MHC interaction (19). The  $\text{COOH}$ -terminal domain of TSST-1 is oriented up and away from the DR1 molecule (Fig. 1A). The TSST-1 molecule covers the entire top of the DR1  $\alpha 1$  domain and about half of the peptide binding groove (Fig. 1, B and C).

Although a continuous surface, the TSST-1:DR1 interface (Fig. 2A) can be usefully divided into three major contact regions: an interdigitation of two loops from TSST-1 (near t30 and t50) with two loops from DR1 (near  $\alpha 18$  and  $\alpha 38$ ) (contact region I), the packing of four  $\beta$  strands of TSST-1 on the top of the  $\alpha$  helix of the  $\alpha 1$  domain of DR1 (contact region II), and an interaction between the antigenic peptide bound on DR1 and two  $\beta$  strands from TSST-1 (contact region III). Twenty-four residues of TSST-1 and 20 residues of DR1 (Table 3), making hydrophobic interactions, hydrogen bonds, and salt bridges, form an extensive contact [ $\sim 1000 \text{ \AA}^2$  buried with the use of a 1.4 Å solvent probe (20)].

Contact region I (Fig. 2B) is centered on Leu<sup>30</sup> of TSST-1, which is surrounded by nonpolar residues (M36, I63, and Y13) (21) of DR1. This leucine is conserved in SEB (L30 of TSST-1 = L45 of SEB) (Table 3) and makes similar contacts to DR1 in the SEB:DR1 interface (7). In both the TSST-1:DR1 and SEB:DR1 interfaces, this leucine is one of the most extensively buried residues ( $159 \text{ \AA}^2$  in TSST-1;  $80 \text{ \AA}^2$  in SEB). To one side (left, Fig. 2B) of the leucine, polar residues (D27 and K58) of TSST-1 potentially hydrogen bond to polar residues (Q18, Y13, and K67) of DR1. On the other side of the leucine (right, Fig. 2B), K39 of DR1 potentially hydrogen bonds to S53 and the main chain carbonyl oxygen of P50 on TSST-1. In the SEB:DR1 interface, the same DR1 K39 formed a very different contact, forming a salt bridge to SEB E67 (7) (Fig. 3). Mutation of DR1 K39 has been shown to disrupt binding of both TSST-1 and SEB (14, 15).

In contact region II, the top face of four turns of the  $\alpha$  helix on the DR1  $\alpha 1$  domain ( $\alpha 57$  to  $\alpha 71$ ) (Fig. 2C), a site also recognized by T cell receptors, is covered by four

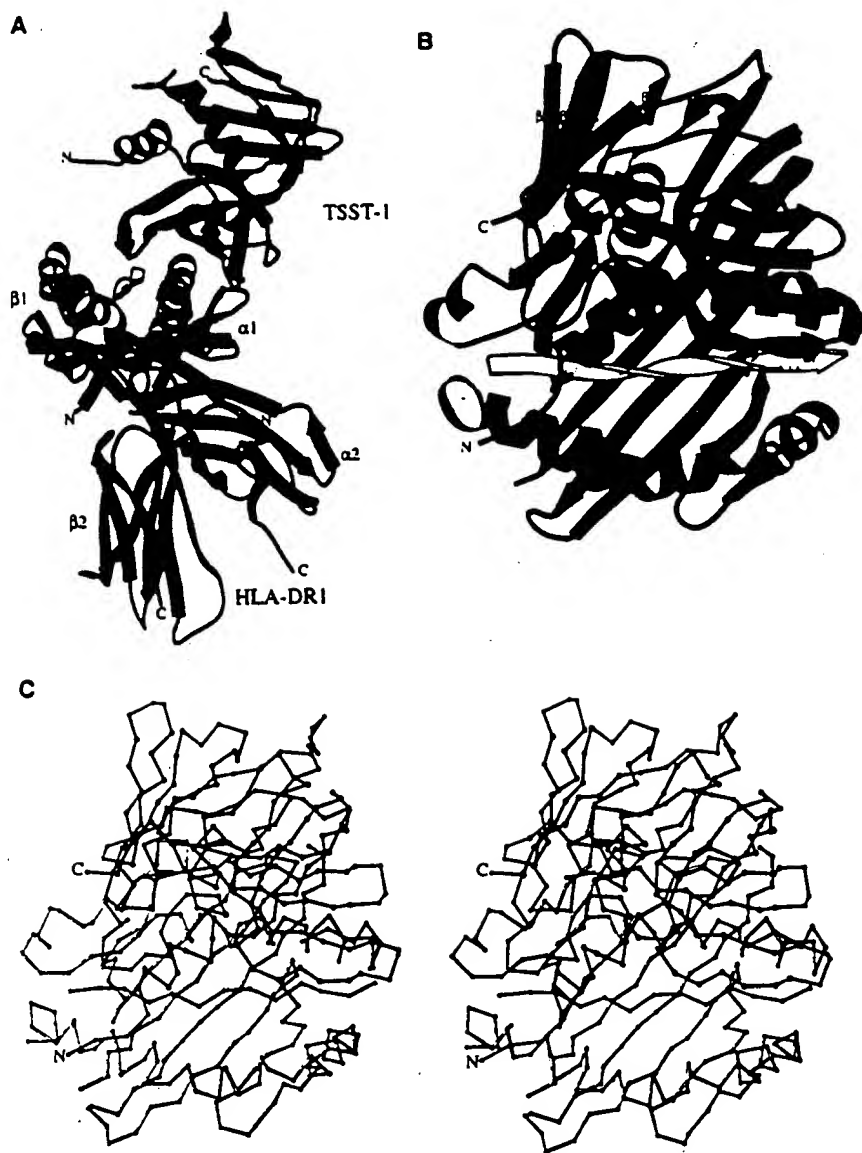


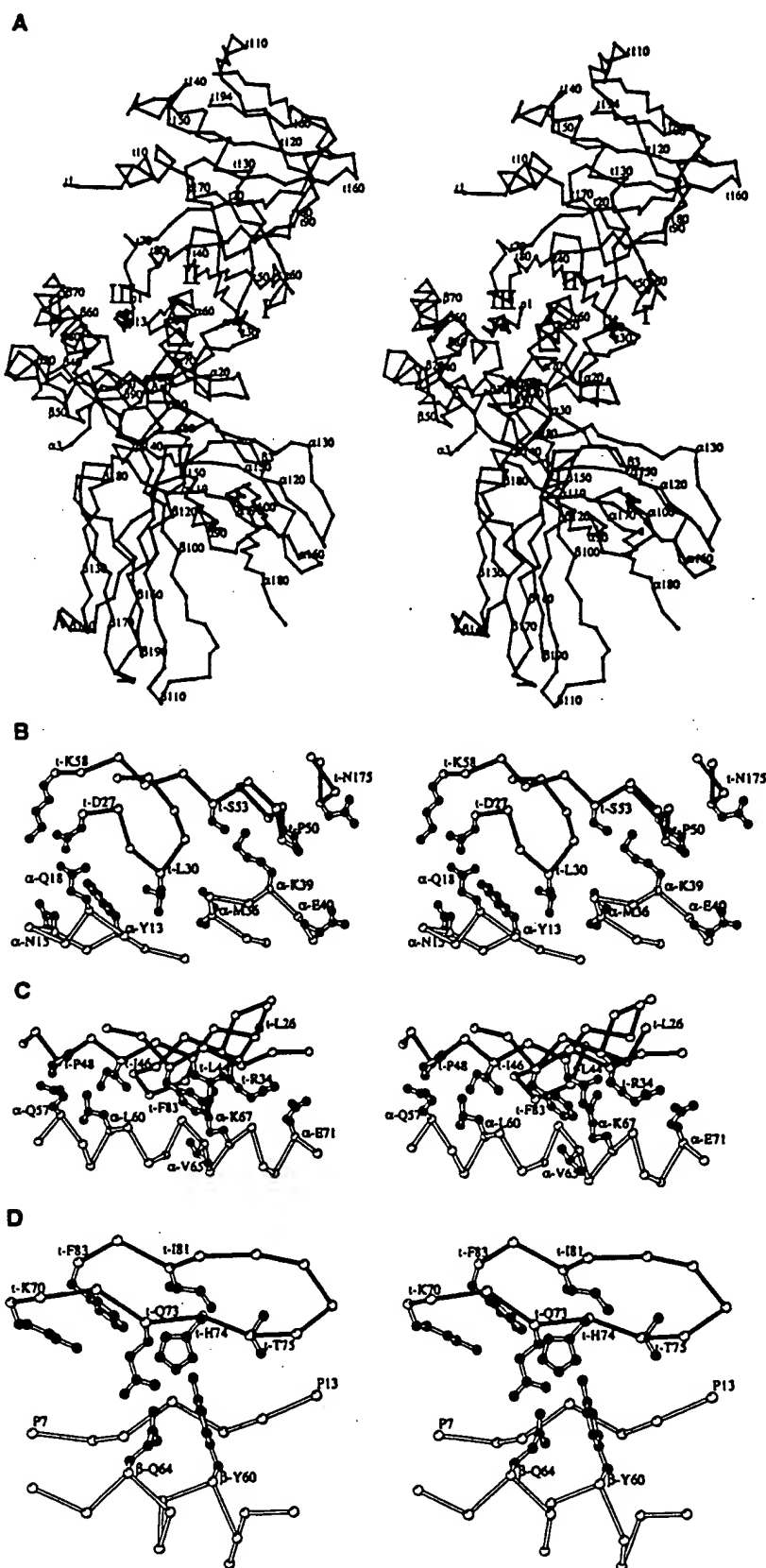
Fig. 1. (A) The TSST-1:DR1 complex [all the figures are generated with MolScript (32)]. The  $\alpha$  and  $\beta$  subunits of DR1 are light blue and blue, respectively, the antigenic peptide is yellow, and TSST-1 is red. (B) The TSST-1:DR1 complex viewed toward the MHC peptide binding site of DR1 [coloring is as in (A)]. Secondary structural elements of TSST-1 ( $\alpha 1$  and  $\alpha 2$  and  $\beta 1$  through  $\beta 12$ ) are marked for comparison with (C). (C) Stereo view of the TSST-1:DR1 complex viewed as in (B). The  $\alpha 1$  and  $\beta 1$  domains of DR1 are in white, the antigenic peptide is shaded, and TSST-1 is black. The  $\alpha 2$  and  $\beta 2$  domains of DR1 are omitted for clarity. The secondary structural elements of TSST-1 are marked by closed circles for the  $\alpha$  carbons: t5 through t14 ( $\alpha 1$ ), t18 through t28 ( $\beta 1$ ), t32 through t37 ( $\beta 2$ ), t41 through t47 ( $\beta 3$ ), t60 through t75 ( $\beta 4$ ), t79 through t89 ( $\beta 5$ ), t101 through t106 ( $\beta 6$ ), t109 through t111 ( $\beta 7$ ), t119 through t124 ( $\beta 8$ ), t125 through t140 ( $\alpha 2$ ), t152 through t158 ( $\beta 9$ ), t162 through t167 ( $\beta 10$ ), t180 through t182 ( $\beta 11$ ), and t187 through t193 ( $\beta 12$ ). C, COOH-terminus; N,  $\text{NH}_2$ -terminus.

$\beta$  strands of TSST-1 ( $\beta 2$ ,  $\beta 3$ ,  $\beta 5$ , and  $\beta 4$ ) (Fig. 1B). Six of the 10 DR1 residues in the contact ( $\alpha 57$ ,  $\alpha 60$ ,  $\alpha 61$ ,  $\alpha 63$ ,  $\alpha 64$ , and  $\alpha 67$ ) when mutated affect T cell stimulation by conventional antigens (8). The same six DR1 residues are contacted by SEB, but the contact is made by SEB disulfide loop residues 94 to 97 (7), which are deleted in TSST-1 (replaced by the short loop between  $\beta 4$  and  $\beta 5$ ) (Fig. 1B). In the TSST-1:DR1 interface, five of the 10 DR1 helical residues are highly conserved in class II MHC sequences and five are polymorphic (22). About 63% of the buried surface in region II is contributed by the conserved DR1 residues, which may be enough to stabilize this contact in TSST-1 complexes with other class II MHC molecules. A cluster of nonpolar residues on the concave surface of the TSST-1  $\beta$  sheet (I42, L44, I46, P50, I81, and F83) (10) interact with most DR1  $\alpha$ -helical residues; at one end of this interface, the charged DR1 residues E71 and K67 potentially form a salt bridge and hydrogen bond with TSST-1 R34 and the main chain at D27, respectively (Fig. 2C). L46 of TSST-1, which is in the center of the apolar core of contact region II (Fig. 2C), is homologous to E67 of SEB, which in the DR1:SEB complex is connected by a salt bridge to K39 in contact region I of DR1.

In contact region III (Fig. 2D), a  $\beta$  loop of TSST-1 ( $\beta 4$  and  $\beta 5$ ) makes a few interactions with the COOH-terminal region of the bound peptides and the top of one turn of the  $\beta 1$  domain  $\alpha$  helix. Residues 7 to 13 (p7 to p13) of the peptide are near TSST-1 residues K70, Q73, I81, and F83, and residues T75 and S76 appear close enough to hydrogen-bond to p13. Q73 of TSST-1 may hydrogen-bond to DR1  $\beta$  chain residues Y60 and Q64 (Fig. 2D). Q73 of TSST-1 is homologous to C93 of SEB. In the SEB:

DR1 interface, that SEB residue (C93) contacts the top of the  $\alpha 1$  domain  $\alpha$  helix and thus resides in contact region II rather than in region III, as in TSST-1:DR1.

Although the structures of TSST-1 and SEB are very similar (9, 10), SEB contacts only DR1 at two regions—on one side of DR1 (contact region I) and on top of the  $\alpha$



**Fig. 2.** (A) Three major contact regions in TSST-1:DR1 are designated by I, II, and III, respectively (33). The  $\alpha$  positions of DR1 are indicated by open circles and those of TSST-1 by closed circles. (B) Contact region I. The DR1 and TSST-1  $\alpha$  chains are indicated by light bonds and dark bonds, respectively. Contact region I is formed by interdigitation of two loops from the DR1 molecule ( $\alpha 13$  to  $\alpha 18$  and  $\alpha 36$  to  $\alpha 39$ ) and two loops from the TSST-1 molecule (t27 to t34 and t42 to t58). Some residues from the COOH-terminal domain of TSST-1 are also located in this region. (C) Contact region II. DR1 and TSST-1  $\alpha$  chains are indicated by light bonds and dark bonds, respectively. Four  $\beta$  strands from the  $\text{NH}_2$ -terminal domain of TSST-1 cover the  $\alpha$  helix from the  $\alpha 1$  domain of DR1. (D) Contact region III. DR1 and TSST-1  $\alpha$  chains are indicated by light bonds and dark bonds, respectively. TSST-1 interacts with the COOH-terminal region of the antigenic peptide (p7 to p13) and some residues from the  $\beta 1$  domain  $\alpha$  helix of DR1.



chain  $\alpha$  helix (contact region II)—whereas TSST-1 has one further contact region, to the bound peptide and the DR1  $\beta$  chain. Both TSST-1 and SEB use homologous leucines (L30 TSST-1 and L45 SEB) to

form contact region I, but TSST-1 uses residues (like L46 and F47) that were part of contact region I in SEB:DR1 to form contact region II on top of the DR1 helix, and TSST-1 uses residues (like Q73) that

were part of contact region II (top of the  $\alpha$  helix) in SEB:DR1 to reach over the top of the peptide and  $\beta$  chain to form contact region III.

Structural models for the interaction of TCRs with superantigens have been proposed on the basis of mutation studies and the three-dimensional structures of SEB, TSST-1, and the SEB:DR1 complex (7, 10). Sites on TSST-1 where mutations affect TCR binding (Fig. 3) form a surface facing up away from the DR1 molecule in the TSST-1:DR1 complex. The very different mode of binding of TSST-1 to class II MHC molecules seen here, relative to SEB, suggests that TCRs may be oriented very differently in complexes with various superantigens (23), yet still may be capable of initiating a signal solely on the basis of crosslinking MHC-bearing membranes to TCR-bearing membranes. Although the structures of the complexes of SEB and TSST-1 with DR1 both suggest that TCRs could simultaneously contact superantigen and DR1 molecules, the TSST-1:DR1 complex also suggests the possibility that TCRs might contact only TSST-1 and be blocked from contacting DR1.

The binding of TSST-1 to class II MHC molecules is known to be affected by changes in the  $\alpha 1$  and  $\beta 1$  domains of DR molecules (14, 24) and to mutations at residues  $\alpha 36$  and  $\alpha 39$  (14, 25), which is consistent with the interface observed in the TSST-1:DR1 crystals (Figs. 1 and 2). A comparison of the structure of the TSST-1:DR1 complex with that of the SEB:DR1 complex (7)

**Tabl 2.** Refinement statistics. TOM/FRDO (31) was used for model building, and X-PLOR (18) was used in the refinement with PARAM19X.PRO as the parameter file. Four refinement steps were carried out with the available 3.5 Å resolution data. The initial molecular replacement model refined as rigid molecules had a value for  $R_{\text{cryst}}$  of 43%. Residues in poor electron density in the map calculated from combined SIR and model phases were eliminated from the model. Cycles of positional and individual  $B$  factor least squares refinement reduced the  $R$  factor to 25% and  $R_{\text{free}}$  to 38%. Improvements in phases allowed the omitted residues to be rebuilt from inspection of  $2F_o - F_c$  and  $F_o - F_c$  electron density maps. After rebuilding, a simulated annealing (3000°) and individual  $B$  factor refinement reduced the value for  $R_{\text{cryst}}$  to 22%. Although the value for  $R_{\text{free}}$  did not drop significantly at this stage, significant improvement of electron density was observed. After rebuilding into the resultant  $2F_o - F_c$  map, the initial  $R$  factor was 38%, and subsequent positional and individual  $B$  factor refinement reduced the  $R$  factor to 22% and  $R_{\text{free}}$  to 35%. As a precaution against model bias in placing side chains, a series of simulated annealing omit maps (18) was examined. The absence of intensity data beyond 3.5 Å resolution limits the effectiveness of this refinement, so that the precision of atomic positions and the certainty of side chain placement is reduced.  $R_{\text{free}}$  was calculated with ~10% of reflections excluded from the refinement. The number of reflections in the refinement was 10,546 (with  $F_{\text{obs}} > 0$ ); the number of reflections in the free set was 1050; the number of atoms in the refinement was 4654; and the number of solvent molecules was 0.

Structural statistics	Before refinement	After partial refinement
$R_{\text{cryst}}$ (10.0 to 3.5 Å)	0.38	0.22
$R_{\text{free}}$ (10.0 to 3.5 Å)	0.38	0.35
Root mean square deviation		
Bond lengths (Å)	0.02	0.018
Bond angles (degrees)	2.7	3.5
Dihedral angles (degrees)	31.0	27.0
Improper torsion (degrees)	1.6	1.5

\* $R_{\text{cryst}}$  and  $R_{\text{free}} = \sum |F_{\text{obs}} - F_{\text{calc}}| / \sum F_{\text{obs}}$  and  $|F_{\text{obs}} - F_{\text{calc}}| / \sum F_{\text{obs}}$ , where  $F_{\text{obs}}$  is the observed structure factor.

**Tabl 3.** The TSST-1:DR1 interface. Underlined residue numbers are also found in the DR1:SEB interface.

TSST-1 residue (SEB residue no.) [buried surface area (Å <sup>2</sup> )]	Location	DR1 contact residues* [buried surface area (Å <sup>2</sup> )]
t-D27† (D42) (35.8)	$\beta 1$	$\alpha$ -Q18 (79.4); $\alpha$ -Y13† (13.8); $\alpha$ -K67† (93.5)
t-S29 (F44) (29.8)	$\beta 1\beta 2$ loop	
t-L30 (L45) (156.9)	$\beta 1\beta 2$ loop	$\alpha$ -M36 (45.0); $\alpha$ -I63 (19.7)
t-G31 (Y46) (34.2)	$\beta 1\beta 2$ loop	
t-S32 (F47) (31.0)	$\beta 2$	$\alpha$ -A64 (54.2)
t-R34† (L49) (93.9)	$\beta 2$	$\alpha$ -E71† (51.5); $\alpha$ -A68 (41.3)
t-I42 (N63) (11.5)	$\beta 3$	
t-L44 (R65) (49.0)	$\beta 3$	
t-I46 (E67) (74.3)	$\beta 3$	$\alpha$ -A61 (26.7); $\alpha$ -Q57 (85.1)
t-F47† (F68) (15.2)	$\beta 3$	$\alpha$ -K39† (120.4)
t-P48 (K69) (60.9)	$\beta 3\beta 4$ loop	$\alpha$ -L60 (53.1)
t-P50 (K71) (68.4)	$\beta 3\beta 4$ loop	$\alpha$ -K39 (120.4); $\alpha$ -K38 (38.5)
t-S53† (A74) (25.4)	$\beta 3\beta 4$ loop	$\alpha$ -K39† (120.4)
t-K58† (-) (17.8)	$\beta 3\beta 4$ loop	$\alpha$ -Q18† (79.4)
t-T69 (Y89) (10.1)	$\beta 4$	
t-K70 (Y90) (39.6)	$\beta 4$	
t-Q73† (C93) (78.3)	$\beta 4$	$\beta$ -Y60† (57.3); $\beta$ -B64† (37.8)
t-H74 (T94) (36.6)	$\beta 4$	
t-T75† (F95) (54.5)	$\beta 4$	p-A13† (61.6)
t-S76† (S96) (14.7)	$\beta 4\beta 5$ loop	p-A13† (61.6)
t-E77 (K97) (21.7)	$\beta 4\beta 5$ loop	
t-I81 (K111) (21.5)	$\beta 5$	
t-F83 (C113) (15.3)	$\beta 5$	$\alpha$ -V65 (37.3)
t-I85 (Y115) (12.8)	$\beta 5$	
Other residues at the contact region with more than 4 Å separation from the TSST-1 residues		$\alpha$ -I72 (25.2) p-A7 (13.6) p-A10 (45.8)

\*van der Waals contact (<~3.8 Å). †Potential hydrogen bond (<~3.5 Å). ‡Potential salt bridge.



**Fig. 3.** Location of TSST-1 residues reported to be involved in TCR interactions. The  $\alpha 1$  and  $\beta 1$  domains of DR1 are in light blue and blue, the antigenic peptide is yellow, and TSST-1 is red. Residues t-Y115, t-E132, t-H135, t-I140, t-H141, and t-Y144, which are important for mitogenic activity of TSST-1 (26) and have been implicated in TCR binding (9, 10), are represented as ball-and-stick models.

reveals that 11 of the 17 DR1 residues in the TSST-1:DR1 interface (underlined in Table 3) are common to the SEB:DR1 interface, despite the overall difference in orientations of the two superantigens on DR1. (Thirteen of the 19 positions on TSST-1 that contact DR1 are homologous to positions on SEB that contact DR1.) Thus, it seems impossible for TSST-1 and SEB to bind simultaneously to DR1, as they would need to occupy the same space. Yet, neither TSST-1 nor SEB appears to be able to completely inhibit the binding of the other (11, 13, 25). One possible explanation for this dilemma would be the existence of a second binding site on DR1 for SEB or TSST-1, but there is no evidence for such a site.

The most striking new observation about superantigen-class II interaction seen in the TSST-1:DR1 complex is that the superantigen covers most of the peptide binding site, contacting all the polymorphic residues on the  $\alpha$  chain  $\alpha$  helix, residues on the bound peptide, and part of the  $\beta$  chain  $\alpha$  helix, across the peptide binding site. This contrasts with our expectation because superantigen activation of T cells is reportedly much less MHC-restricted and peptide-dependent than peptide antigen-induced activation. It suggests that TSST-1 binding to DR1 may be in part peptide-dependent. Recent binding measurements between superantigens and DR molecules on different cell types suggest that different subsets of HLA-DR molecules may bind TSST-1 and SEB (25). Peptide-dependent binding offers a possible mechanism for superantigens to distinguish different subsets of DR1 molecules and that in turn could account for the inability of TSST-1 to inhibit completely the binding of SEB to DR1. Superantigen activation dependent on peptide (and hence also MHC allele) would allow a pathogen to direct T cell activation by its antigens or by host antigens during infections, with potential consequences for inducing specific autoreactivity.

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mixture was then transferred to pre-chilled ultracentrifugation tubes and subjected to 35,000g for 1 hour at 4°C. The cleared supernatants were then adjusted to 50 ml containing a 2% final concentration of ampholytes (Ampholine, 3.5-10, Pharmacia LKB, Uppsala, Sweden). The mixture was then transferred into a preparative isoelectric focusing cell (Rotofor, Bio-Rad Laboratories, Richmond, CA) and focused at 12 W for 5 hours at 4°C. Fractions were then collected, and those containing DR (pH 4.0 to 5.5) were pooled and dialyzed against 50 volumes of 10 mM Tris-HCl (pH 7.5). The sample was then concentrated to 2 ml by vacuum dialysis against 10 mM Tris-HCl (pH 7.5) and further purified by size exclusion chromatography (SEC-3000; 5  $\mu$ m; 7.5 cm by 30 cm, Beckman Instruments). The DR peak was collected and re-concentrated to >10 mg/ml by vacuum dialysis as above.

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33. Another contact is found in the crystal between a symmetrically related TSST-1 molecule and the TSST-1:DR1 complex. Of the six TSST-1 residues implicated in TCR recognition by mutagenesis (Y115, E132, H135, I140, H141, and Y144) (26), two (Y115 and Y144) are in the TSST-1:TSST-1 contact and three (H135, I140, and H141) are in its immediate vicinity.
34. We thank D. H. Ohlendorf, J. H. Brown, and L. J. Stern for the coordinates of TSST-1 and DR1; N. Ramesh and R. S. Geha for an initial sample of purified TSST-1; P. Klimovitsky and A. Haykov for technical assistance; and M. Pietras for large-scale production of tissue culture cells. Discussions with T. S. Jardetzky, D. N. Garboczi, and A. Seth and help from D. C. Rees, P. J. Bjorkman, S. E. Ryu, M. J. Eck, R. S. Brown, R. Nolte, and C. Garnett are appreciated. J.K. acknowledges support by the Howard Hughes Medical Institute (HHMI) and NIH. R.G.U. is supported by the Irving Institute for Medical Research. D.C.W. is an investigator of HHMI. Research supported by an NIH grant to D.C.W. Coordinates will be deposited in the Protein Data Bank and are available before their release by e-mail (kim@xtal.harvard.edu).

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## Subsets of HLA-DR1 Molecules Defined by SEB and TSST-1 Binding

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Superantigens bind to major histocompatibility complex class II molecules on antigen-presenting cells and stimulate T cells. *Staphylococcus aureus* enterotoxin B (SEB) and toxic shock syndrome toxin-1 (TSST-1) bind to the same region of human lymphocyte antigen (HLA)-DR1 but do not compete with each other, which indicates that they bind to different subsets of DR1 molecules. Here, a mutation in the peptide-binding groove disrupted the SEB and TSST-1 binding sites, which suggests that peptides can influence the interaction with bacterial toxins. In support of this, the expression of the DR1 molecule in various cell types differentially affected the binding of these toxins.

Superantigens (SAGs) are T cell mitogens produced by a variety of bacteria and viruses (1). The formation of a trimolecular complex between SAGs, major histocompatibility

complex (MHC) class II molecules, and the T cell receptor (TCR) leads to the activation of T cells in a  $V_{\beta}$ -restricted fashion (2). The most studied superantigens of

## Monoclonal antibody-targeted superantigens: A different class of anti-tumor agents

(staphylococcal enterotoxins/cytotoxic T cells/colon cancer cells)

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**ABSTRACT** The bacterial superantigen staphylococcal enterotoxin (SE) A (SEA) directs cytotoxic T lymphocytes (CTLs) expressing particular sequences of the T-cell receptor (TCR)  $\beta$  chain to lyse tumor cells expressing major histocompatibility complex (MHC) class II molecules, which serve as receptors for SEs. We now report that chemical conjugates of SEA and the colon carcinoma-reactive monoclonal antibodies (mAbs) C215 or C242 mediate T cell-dependent destruction of colon carcinoma cells lacking MHC class II molecules. SEA was covalently linked to the mAbs C215 and C242 via a PEG-based hydrophilic spacer. The C215-SEA conjugate targeted CD4<sup>+</sup> as well as CD8<sup>+</sup> CTLs to lyse a panel of colon carcinoma cells lacking MHC class II molecules. T-cell recognition of mAb-SEA conjugates was SEA specific, since SEB-selective T-cell lines with potent cytotoxic activity towards Raji cells coated with SEB did not respond to the C215-SEA conjugate. Unconjugated SEA did not induce T-cell lysis of MHC class II<sup>+</sup> colon carcinoma cells but efficiently directed CTLs against MHC class II<sup>+</sup> Raji cells and certain interferon-treated MHC class II<sup>+</sup> colon carcinoma cells. These results suggest that SEA-mAb conjugates retain the SEA-related selectivity for certain TCR  $\beta$ -chain variable region ( $V_{\beta}$ ) sequences but, in contrast to unconjugated SEA, mediate the TCR interaction in a MHC class II-independent manner. The cytotoxic activity mediated by C215-SEA and C242-SEA conjugates was blocked by excess of C215 mAb and C242 mAb, respectively, showing that the specificity in the targeting of mAb-SEA conjugates is defined by the antigen reactivity of the mAb. These results demonstrate that bacterial superantigens may be successfully conjugated to mAb with preserved T cell-activating capacity. The circumvention of MHC class II binding of SEs by conjugation to mAb suggests that such conjugates may find general application as antitumor agents, taking advantage of the extreme T cell-activating potency of superantigens.

The collection of superantigens consists of bacterial exoproteins, such as the structurally related staphylococcal and streptococcal exotoxins, but also endogenous self superantigens, including the mammary tumor virus-encoded Mls antigens (1-3). They are characterized by the capacity to stimulate in a major histocompatibility complex (MHC) class II-dependent manner a high frequency of T cells bearing particular T-cell receptor (TCR)  $\beta$ -chain variable segments ( $V_{\beta}$ ) (1, 4-10). Studies on the staphylococcal enterotoxins (SEs) A and B (SEA and SEB) and toxic shock syndrome toxin 1 have shown high-affinity binding to MHC class II molecules (4-6, 10-12). SEA, SEB, and toxic shock syndrome toxin 1 bind to a variety of different MHC class II isotypes and the binding seems to involve conserved peptide sequences expressed on both the MHC class II  $\alpha$  and  $\beta$  chains (9-13). T cells recognizing the MHC

class II-SE complex are activated to proliferation, cytokine production, and cytotoxicity (14-19). The SE-dependent cell-mediated cytotoxicity (SDCC) results in elimination of MHC class II-expressing SE-presenting target cells (17-19). Studies on fresh MHC class II<sup>+</sup> leukemic cells have suggested that the SDCC mechanisms may be a useful tool for therapeutic elimination of MHC class II<sup>+</sup> tumor cells (16). However, since MHC class II-expressing tumor types only represent a minority of the most frequent human tumors and systemic T-cell activation is expected to result in severe toxicity, it seems reasonable to assume that the SDCC mechanism will not have general application in the treatment of human malignant diseases. During the last decade monoclonal antibodies (mAbs) have been evaluated for tumor therapy; either as native antibodies or conjugated to radioactive isotopes, cytotoxic drugs, or plant toxins (20-23). Recent attempts have also included polyclonal activation of T lymphocytes by antibody heteroconjugates simultaneously recognizing tumor cells and the CD3/TCR complex on T cells (24-26). The direct binding of antibody heteroconjugates to the T cell may be a major drawback *in vivo*, counteracting mAb localization at the tumor site. In this report we demonstrate that conjugates between SEA and mAbs recognizing human colon cancer enable T cells to lyse colon carcinoma cells *in vitro*. The mAb-SEA conjugates direct cytotoxic T lymphocytes (CTLs) against target cells expressing the mAb-defined cell-surface antigen independent of their MHC expression. In contrast to antibody heteroconjugates, the mAb-SEA conjugates do not engage T cells prior to binding to the target cell. We believe that mAb-superantigen-based conjugates represent a novel and powerful approach to tumor therapy, which may have significant advantages in comparison with earlier described antibody-based therapies.

### MATERIALS AND METHODS

**Reagents.** SEB was purchased from Toxin Technology (Madison, WI). Recombinant SEA was expressed in *Escherichia coli* and purified to homogeneity as described elsewhere (ref. 27). The following mAbs were used to detect monomorphic determinants on human MHC class II: HLA-DR, L243 and D1-12; HLA-DP, B7/21; and HLA-DQ, SK10 (HLA-Qw1 and -Qw3), BT3/4 (HLA-DQw1), and SFR16-P1.2 (HLA-DQw2 and -DQw3). The sources of these mAbs have been reported recently (27). The mAbs C215 (IgG2a) and C242 (IgG1) reacting with human colon cancer were obtained from L. Lindholm, Pharmacia Canag (Göteborg, Sweden). Rabbit anti-SEA serum was obtained from Phar-

Abbreviations: SE, staphylococcal enterotoxin; SEA and SEB, SEs A and B; mAb, monoclonal antibody; TCR, T-cell receptor; CTL, cytotoxic T lymphocyte; MHC, major histocompatibility complex;  $V_{\beta}$ ,  $\beta$ -chain variable regions; SDCC, SE-dependent cell-mediated cytotoxicity; FITC, fluorescein isothiocyanate.

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macia. Fluorescein isothiocyanate (FITC)-labeled swine anti-rabbit and rabbit anti-mouse immunoglobulins were purchased from Dakopatts (Glostrup, Denmark).

**Preparation of mAb-SEA Conjugates.** Recombinant SEA was coupled to the C215 mAb or C242 mAb by the use of *N*-succinimidyl 3-(2-pyridyldithio)propionate (SPDP, Pharmacia) and a 24-atom-long PEG-based hydrophilic spacer (*N*-hydroxysuccinimide ester of 17-iodoacetyl-3,6,9,12,15-pentaoxaheptadecanoic acid) as recently described (ref. 28). Briefly, the  $\epsilon$ -amino groups of the lysines in the mAb were randomly substituted with the PEG-based spacer, which resulted in 7–18 coupled spacers per mAb. One or two mercapto groups were substituted on the  $\epsilon$ -amino groups of lysines in SEA by reaction with the SPDP reagent (29). The spacers ended with reactive iodine groups which reacted with the mercapto groups introduced on SEA, resulting in the formation of stable thioether linkages. The synthesized mAb-SEA conjugate was fractionated on a Superdex 200 HR 16/50 column (Pharmacia) and was eluted with 2 mM phosphate buffer, pH 7.5/0.15 M NaCl. Fractions with the desired product were pooled and analyzed by SDS/PAGE on Phast-Gel5 gradient 4-15 and silver staining (Pharmacia). The conjugates contained zero to three SEA molecules per mAb molecule (average one for C215-SEA and two for C242-SEA).

**$^{125}$ I-Labeled SEA ( $^{125}$ I-SEA) and C215- $^{125}$ I-SEA Binding Assays.** SEA or C215-SEA (5–10  $\mu$ g) was mixed with 0.5–1.0 mCi (1 Ci = 37 GBq) of  $^{125}$ I (carrier-free NaI, 105 mCi/ml; DuPont/NEN) in 200  $\mu$ l of phosphate-buffered saline (PBS). One Iodo-Bead (Pierce) was added to the mixture, and after 15 min of incubation at room temperature, 2-mercaptoethanol was added to stop the reaction. Iodinated proteins were separated from free iodine by gel filtration (PD-10 Sephadex G-25M, Pharmacia). When evaluating the inhibition of  $^{125}$ I-SEA and C215- $^{125}$ I-SEA to Raji cells by SEA and C215-SEA, respectively,  $10^6$  Raji cells in 50  $\mu$ l of PBS with 1% bovine serum albumin were incubated with various concentrations of unlabeled inhibitor for 30 min at room temperature. Fifty microliters of  $^{125}$ I-SEA and 50  $\mu$ l of C215- $^{125}$ I-SEA were then

added, and the mixture was further incubated for 15 min. Cell-associated radioactivity was separated from free  $^{125}$ I-SEA and C215- $^{125}$ I-SEA by centrifugation of the Raji cells on a 40% Ficoll-Paque (Pharmacia) cushion.

**Cell Lines.** The B-cell lymphoma line Raji and the colon carcinoma lines SW620, COLO 205, and WiDr were obtained from American Type Culture Collection and cultured in R-medium (RPMI 1640 medium (GIBCO) supplemented with 10% fetal calf serum, 1 mM nonessential amino acids, 50  $\mu$ M 2-mercaptoethanol, and 1 mM pyruvate (Flow Laboratories)). T-cell lines were established by stimulation of human peripheral blood lymphocytes with SEA or SEB (1 ng/ml) as detailed earlier (15, 16). These T-cell lines were all >99% CD3<sup>+</sup>, CD4<sup>+</sup> and CD8<sup>+</sup> sublines were established after separation by positive selection with magnetic beads pre-coated with anti-CD4 or anti-CD8 mAb (Dynabeads M-450, Dynal A/S, Oslo, Norway). These sublines were >92% pure with respect to CD4 or CD8.

**Cytotoxicity Assay.** Cytotoxicity was measured at various effector/target cell ratios in a standard 4-hr  $^{51}$ Cr-release assay as described (15). SEs or conjugates were added at various concentrations directly into the assay or were used for preincubation of target cells. Preincubation was performed at 37°C for 30 min followed by extensive washing of the cells.

**Analysis by Flow Cytometry.** Flow cytometric analyses were performed with indirect immunofluorescence and with standard settings on a FACStarPLUS flow cytometer (Becton Dickinson).

## RESULTS

**Binding Characteristics of the C215-SEA Conjugate.** Binding of mAb C215 and the C215-SEA conjugate to COLO 205 cells, which express the C215 antigen but not MHC class II molecules, was analyzed by flow cytometry with FITC-labeled anti-mouse IgG antibodies. The binding of the conjugate to COLO 205 cells was similar to that of the parental mAb (Fig. 1A). Extensive titrations of unconjugated mAb and C215-SEA

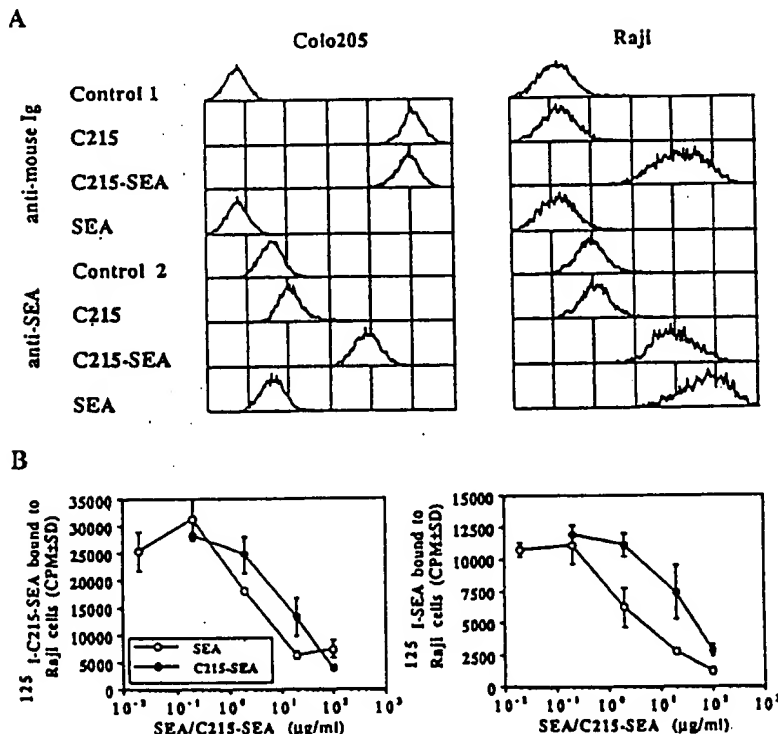


FIG. 1. Binding of C215-SEA, C215 mAb, and SEA to COLO 205 and Raji cells. (A) Fluorescence-activated cell sorter analysis on binding of C215-SEA conjugate, C215 mAb, and SEA to COLO 205 and Raji cells was performed by the use of FITC-labeled rabbit anti-mouse immunoglobulin (control 1) or rabbit anti-SEA sera/FITC-labeled swine anti-rabbit immunoglobulin (control 2). (B) Inhibition of  $^{125}$ I-SEA and C215- $^{125}$ I-SEA binding to Raji cells by unlabeled SEA and C215-SEA. The inhibitors were added 30 min before the labeled reagent.

conjugate demonstrated similar binding characteristics, with saturated binding detected at about 3  $\mu\text{g}/\text{ml}$  (data not shown). The C215-SEA conjugate, but not unconjugated SEA or C215 mAb, was detected on COLO 205 cells as analyzed by the use of rabbit anti-SEA antibodies and FITC-labeled swine anti-rabbit immunoglobulin (Fig. 1A). We demonstrated earlier (4) that SEA bound with high affinity to MHC class II molecules on Raji cells. Fluorescence-activated cell sorter analysis showed that SEA and C215-SEA, but not unconjugated C215, bound strongly to Raji cells (Fig. 1A). The binding of C215-SEA to Raji cells was efficiently blocked by SEA but not by C215 (data not shown). Thus, in addition to mAb specificity, the C215-SEA conjugate has retained the capacity of SEA to bind to cells expressing MHC class II molecules. To compare the relative MHC class II binding affinity of SEA and C215-SEA, respectively, we utilized a cell-binding assay with  $^{125}\text{I}$ -SEA and C215- $^{125}\text{I}$ -SEA. Inhibition studies showed that  $^{125}\text{I}$ -SEA was displaced in a dose-dependent manner by SEA and C215-SEA mAb (Fig. 1B). Similarly, C215- $^{125}\text{I}$ -SEA binding to Raji cells was efficiently blocked by SEA and C215-SEA, which indicates that the C215-SEA binding is specific for the MHC class II molecule (Fig. 1B). Assuming that the C215-SEA conjugate contains about 15% SEA, the conjugate apparently displays identical MHC class II binding as SEA on a molar basis.

**T-Cell Targeting by the C215-SEA Conjugate.** The C215-SEA conjugate efficiently directed SEA-responsive CTLs to mediate cytotoxicity against the SW620 colon carcinoma cells, whereas a mixture of unconjugated SEA and C215 mAb had no effect (Fig. 2). Cytotoxicity against SW620 cells was

induced by C215-SEA at effector-to-target ratios as low as 3:1, while unconjugated SEA and C215 mAb lacked effect even at 30:1. Lysis was recorded at 3  $\mu\text{g}$  of the conjugate per ml, whereas SEA at 1000-fold higher concentrations only had marginal effects (Fig. 2). The SW620 cell line did not constitutively or after interferon treatment express surface MHC class II molecules, as analyzed by immunoprecipitation and flow cytometry with a panel of mAbs against the HLA-DR, HLA-DP, and HLA-DQ isotypes (27). Furthermore, Northern blot analysis demonstrated absence of HLA-DR $\alpha$ , HLA-DR $\beta$ , invariant chain, and HLA-DZ $\alpha$  transcripts in SW620 cells (27). C215-SEA conjugate-induced cytotoxicity was observed against several MHC class II<sup>+</sup> C215<sup>+</sup> colon carcinoma cell lines, including WiDr, COLO 205, and SW620 (Fig. 2). Unconjugated SEA (Fig. 2) and C215 mAb (data not shown) demonstrated only marginal effect on MHC class II<sup>+</sup> colon carcinoma cell lines, while SEA induced CTL targeting against MHC class II<sup>+</sup> Raji cells (Fig. 2). CTL targeting against Raji cells was efficiently induced by SEA at 0.003 ng/ml, whereas C215-SEA conjugate at 30 ng/ml was required to induce a comparable half-maximal cell lysis, indicating an extremely low efficiency of the C215-SEA conjugate against MHC class II<sup>+</sup> C215<sup>+</sup> cells compared with SEA.

To analyze the influence of concomitant expression of C215 and MHC class II molecules on a target cell in comparison with separate expression of either of these molecules, we used interferon treatment of COLO 205 cells to induce surface MHC class II expression. Dose-response analysis with untreated MHC class II<sup>+</sup> COLO 205 cells showed

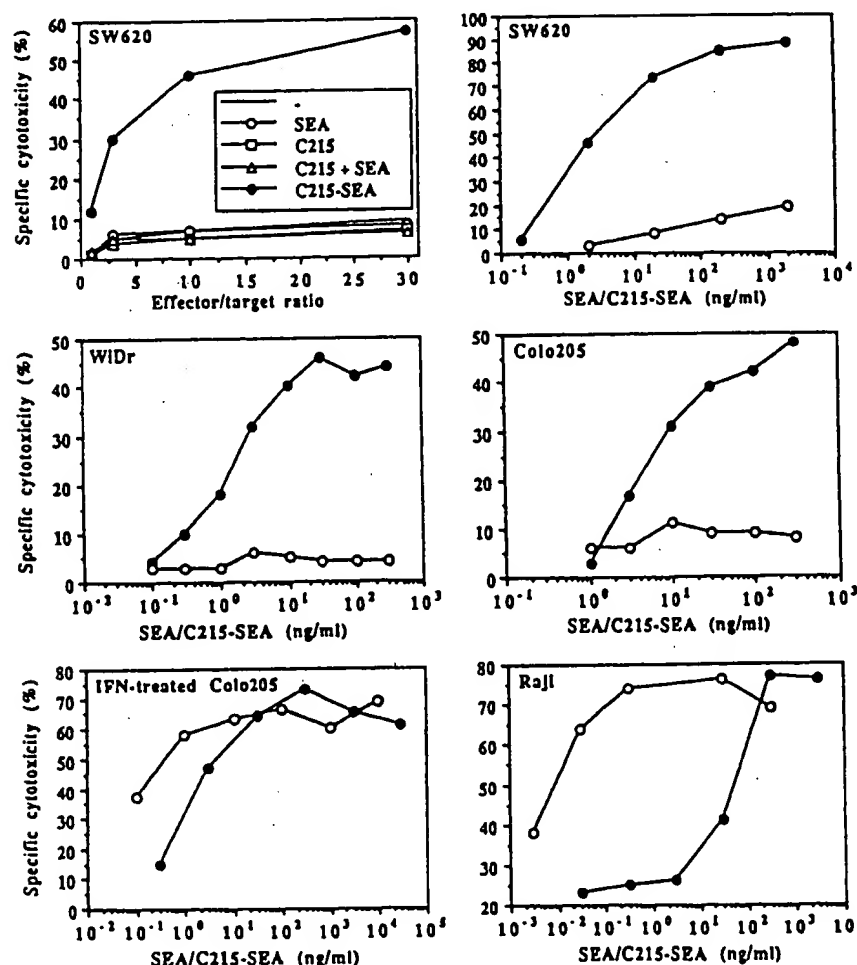


FIG. 2. C215-SEA directs CTLs against MHC class II<sup>+</sup> colon carcinoma cells. (Top Left) Effect of SEA-responsive CTLs against SW620 cells at various effector-to-target ratios in the absence (—) or presence of C215-SEA, SEA, C215, and a mixture of C215 and SEA (C215+SEA) at a concentration of 1  $\mu\text{g}/\text{ml}$  of each additive. Other panels show the capacity of C215-SEA and SEA to target SEA-responsive CTLs against the C215<sup>+</sup> MHC class II<sup>+</sup> colon carcinoma cell lines SW620, COLO 205, and WiDr; MHC class II<sup>+</sup> C215<sup>+</sup> interferon-treated COLO 205 cells; and C215<sup>+</sup> MHC class II<sup>+</sup> Raji cells. Effector-to-target ratio was 30:1. Addition of unconjugated C215 mAb at several concentrations did not induce any CTL targeting against these cell lines. Fluorescence-activated cell sorter analysis on SW620 cells, COLO 205, and WiDr cells using mAbs against HLA-DR, -DP, and -DQ failed to detect any surface MHC class II expression, whereas abundant expression of HLA-DR, -DP, and -DQ was detected on Raji cells and HLA-DR and -DP were detected on interferon-treated COLO 205 cells. COLO 205 cells were treated with 1000 units of recombinant  $\gamma$  interferon per ml for 48 hr prior to use in the CTL assay.

Table 1. CD4<sup>+</sup> and CD8<sup>+</sup> CTLs lyse colon carcinoma cells presenting the C215-SEA conjugate

Effector*	Target	% cytotoxicity		
		Control	SEA	C215-SEA
CD4 <sup>+</sup>	SW620	2	5	50
CD4 <sup>+</sup>	Raji	0	41	43
CD8 <sup>+</sup>	SW620	0	1	23
CD8 <sup>+</sup>	Raji	2	72	68

\*The CTLs (SEA-3) were used at effector-to-target ratio of 30:1 in the absence (control) or presence of SEA and C215-SEA at 1  $\mu$ g/ml.

sensitivity to lysis at low concentrations of the C215-SEA conjugate but resistance to unconjugated SEA and C215 mAb (Fig. 2). Interferon  $\gamma$  treatment of COLO 205 cells resulted in strong expression of HLA-DR and HLA-DP molecules (27) and sensitivity to CTL lysis at similar concentrations of SEA and C215-SEA (Fig. 2).

**C215-SEA Conjugate Targets CD4<sup>+</sup> and CD8<sup>+</sup> SEA-Responsive CTLs but Not SEB-Responsive CTLs.** Both CD4<sup>+</sup> and CD8<sup>+</sup> CTLs mediated conjugate-dependent cytotoxicity against human colon carcinoma cells (Table 1). Unconjugated SEA failed to induce lysis of SW620 cells but targeted CD4<sup>+</sup> and CD8<sup>+</sup> CTL against MHC class II<sup>+</sup> Raji cells (Table 1). C215-SEA conjugate efficiently targeted SEA-responsive CTLs against SW620 and Raji cells but failed to target SEB-responsive CTLs (Fig. 3). In contrast, the SEB-responsive CTLs demonstrated strong cytotoxicity against SEB-coated Raji cells (Fig. 3).

**Specificity of the mAb-SEA Conjugate Is Defined by the mAb.** To demonstrate that the target selectivity of the mAb-SEA conjugate is entirely dependent on the mAb specificity, we performed criss-cross inhibition experiments with unconjugated C215 and C242 mAbs and C215-SEA and C242-SEA conjugates. Cytotoxicity mediated by C215-SEA and C242-SEA was blocked by addition of excess unconjugated C215

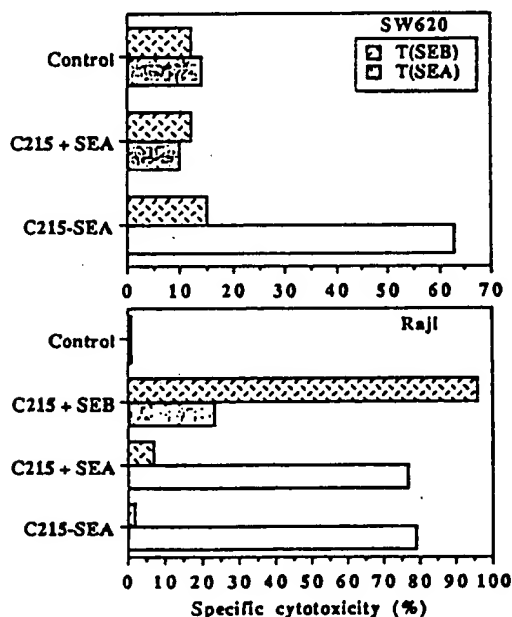


FIG. 3. Lysis of C215-SEA-coated colon carcinoma cells is mediated by SEA but not SEB-responding CTLs. Autologous SEA- and SEB-selective T-cell lines were used at an effector-to-target ratio of 10:1 against SW620 and Raji target cells in the absence (control) or presence of C215-SEA conjugate, a mixture of unconjugated C215 mAb and SEA (C215+SEA), or unconjugated C215 mAb and SEB (C215+SEB) at a concentration of 1  $\mu$ g/ml of each additive.

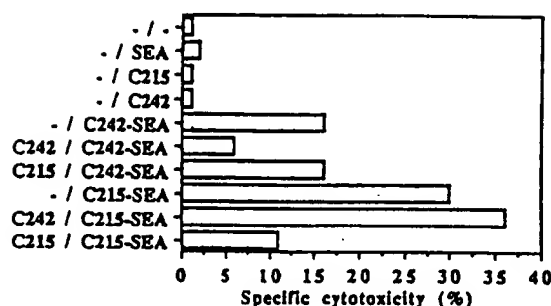


FIG. 4. C215-SEA- and C242-SEA-induced CTL targeting against colon carcinoma cells depends on the antigen selectivity of the mAb. Lysis of COLO 205 cells by a SEA-responsive CTL line in the presence of C215-SEA and C242-SEA conjugates (3  $\mu$ g/ml) is blocked by addition of unconjugated C215 and C242 mAbs (30  $\mu$ g/ml), respectively. The unconjugated mAbs or control medium (-) were added to the target cells 10 min prior to addition of the conjugates.

and C242, respectively but was not influenced by addition of the irrelevant mAb binding to the same target cell (Fig. 4) or high concentrations of isotype-specific control antibodies (data not shown).

## DISCUSSION

CTLs with specificity for antigens expressed on tumor cells have been demonstrated in patients with malignant melanoma and renal cancer (30, 31). However, they are in most cases infrequent and obviously not capable of protecting the host against the growing tumor. The superantigen SEA allows activation of a frequency of T cells (>10%) even higher than that observed during the response to allogeneic MHC in organ transplantation. Since the latter inevitably results in rejection of the transplant, utilization of SEA to direct a high frequency of T cells towards a tumor may hopefully ensure a similar outcome. In this paper we describe such an approach to tumor therapy. Conjugation of SEA to mAb directed against human colon carcinomas provided an agent that was able to selectively target SEA-responsive CTLs against the tumor cells. Earlier studies in our and other laboratories have demonstrated that binding of SEA to MHC class II molecules is a prerequisite for subsequent activation and targeting of T cells (4-6, 15). The SEA-mAb-mediated cytotoxicity apparently is MHC class II independent and does not require antigen-specific effector CTLs. The specificity at the target level is defined by the mAb and at the CTL level by the expression of relevant TCR V $\beta$  sequences, suitable for interaction with SEA.

The SW620 colon carcinoma cell line, which lacked mRNA transcripts for HLA-DR $\alpha$ , HLA-DR $\beta$ , HLA-DZ $\alpha$ , and invariant chain and failed to express surface MHC class II antigens as analyzed by either immunoprecipitation or flow cytometry (27) efficiently presented C215-SEA but not SEA to CTLs. Conjugate-dependent killing not only was restricted to SW620 cells but also was recorded for MHC class II<sup>-</sup> COLO 205 and WiDr cell lines as well as freshly isolated MHC class II<sup>-</sup> human colon carcinoma cells (data not shown). The existence of MHC class II-independent T-cell activation induced by bacterial superantigens is supported by recent studies by Fleischer and co-workers (32). They demonstrated that SEB bound to silica beads activated T cells, provided that CD8- or CD2-mediated costimulatory signals were delivered. It is reasonable to suggest that soluble SEA interacts with insufficient low affinity TCR V $\beta$  to activate T cells, but when presented in multivalent form on a cell surface or bead, an interaction with enhanced avidity is provided. Delivering costimulatory signals through the adhesion structures



LFA-1/ICAM-1, CD2/LFA-3, or CD8 may play an important role in exceeding the activation threshold (19, 32).

In comparison with unconjugated SEA, the C215-SEA conjugate retains similar MHC class II binding ability but has about 0.1% activity in MHC class II-dependent CTL targeting. This may be interpreted as a possible sterical hindrance by the conjugated C215 mAb when SEA is bound to MHC class II molecules, whereas binding to C215\* on a cell surface by the mAb allows an efficient interaction between SEA and the TCR on the effector cell. In a therapeutic situation, presentation of the conjugate on normal MHC class II-expressing cells such as monocytes, B cells, and activated T cells is undesirable. Binding to normal cells would prevent the conjugate from reaching the tumor, and normal MHC class II\* cells have been shown to be sensitive to SDCC (16). Although the present conjugation procedure apparently has markedly reduced the SDCC function of the C215-SEA conjugate, it would be of importance to further perturb MHC class II-dependent CTL activity by reducing the binding affinity of the C215-SEA conjugate for MHC class II molecules. We have recently demonstrated that a recombinant C-terminal fragment of SEA contains MHC class II binding determinants (G.H., unpublished data). Similarly, studies on SEC1 and toxic shock syndrome toxin 1 support a C-terminal location for the MHC class II binding epitopes (33, 34). The determination of the amino acids necessary for MHC class II binding may provide a rationale to obtain mAb-SEA conjugates with preserved T cell-activating properties but totally devoid of binding to MHC class II molecules.

Antibody heteroconjugates and hybrid mAbs reacting with tumor cells and epitopes involved in T-cell activation, including the CD3-TCR complex, CD2, or CD28, have been used to target T cells to kill tumor cells *in vitro* (24–26, 35, 36). However, bispecific mAbs have several limitations as therapeutic agents: (i) the ability to directly bind to the T cells will ultimately lead to capture of the intravenously administered mAb in peripheral blood and perturb tissue penetration, (ii) binding to T cells in the absence of proper cross-linking by the target cell may lead to anergy (37) or cell death (38), and (iii) activation of an excessive number of T cells by pan-T-cell heteroconjugates may result in a cytokine-related shock syndrome and suppression of specific immunity dealing with infectious pathogens (39). In contrast, mAb-SEA conjugates do not suffer from these limitations. The ability of the conjugate to efficiently interact with T cells only when bound to the tumor cell surface allows effective tissue penetration and avoids unwanted systemic T-cell activation. Moreover, local production of lymphokines by T cells activated in the tumor area may be expected to result in a beneficial inflammatory response with direct effects on the tumor cells as well as recruitment of new anti-tumor effector cells in a cascade fashion. SEA is an extremely efficient inducer of interleukin 2, tumor necrosis factor, and  $\gamma$  interferon (14, 40). The activation of a limited fraction of T cells bearing the proper TCR V $\beta$  sequences preserves a large portion of the T-cell repertoire for dealing with specific immunity. Recently attempts to target antigen-specific CD4\* T cells against tumor cells have been made with conjugates of mAbs and recall antigens such as keyhole limpet hemocyanin (41) and purified protein derivative (42). These mAb-antigen conjugates allowed presentation of relevant processed antigenic peptide fragments on MHC class II molecules and retargeting of CTLs to the tumor cells (41, 42). The recruited T cells are primarily of the CD4 type, and their frequency is significantly lower than the responding to SEA. Moreover, the therapeutic use of such mAb-antigen conjugates is limited to MHC class II\* tumor cells, and, in contrast to the mAb-SEA conjugates, they do not have a general application for treating MHC class II\* tumors.

The mAb-SEA conjugates described in this study represent a novel class of anti-tumor agents based on conjugation of a superantigen to a tumor-reactive mAb. Development of superantigen-mAb-based agents may serve as an important immunotherapeutic strategy for treatment of malignant diseases that have escaped the host immune response.

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